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AMERICAN JOURNAL OF OPHTHALMOLOGY

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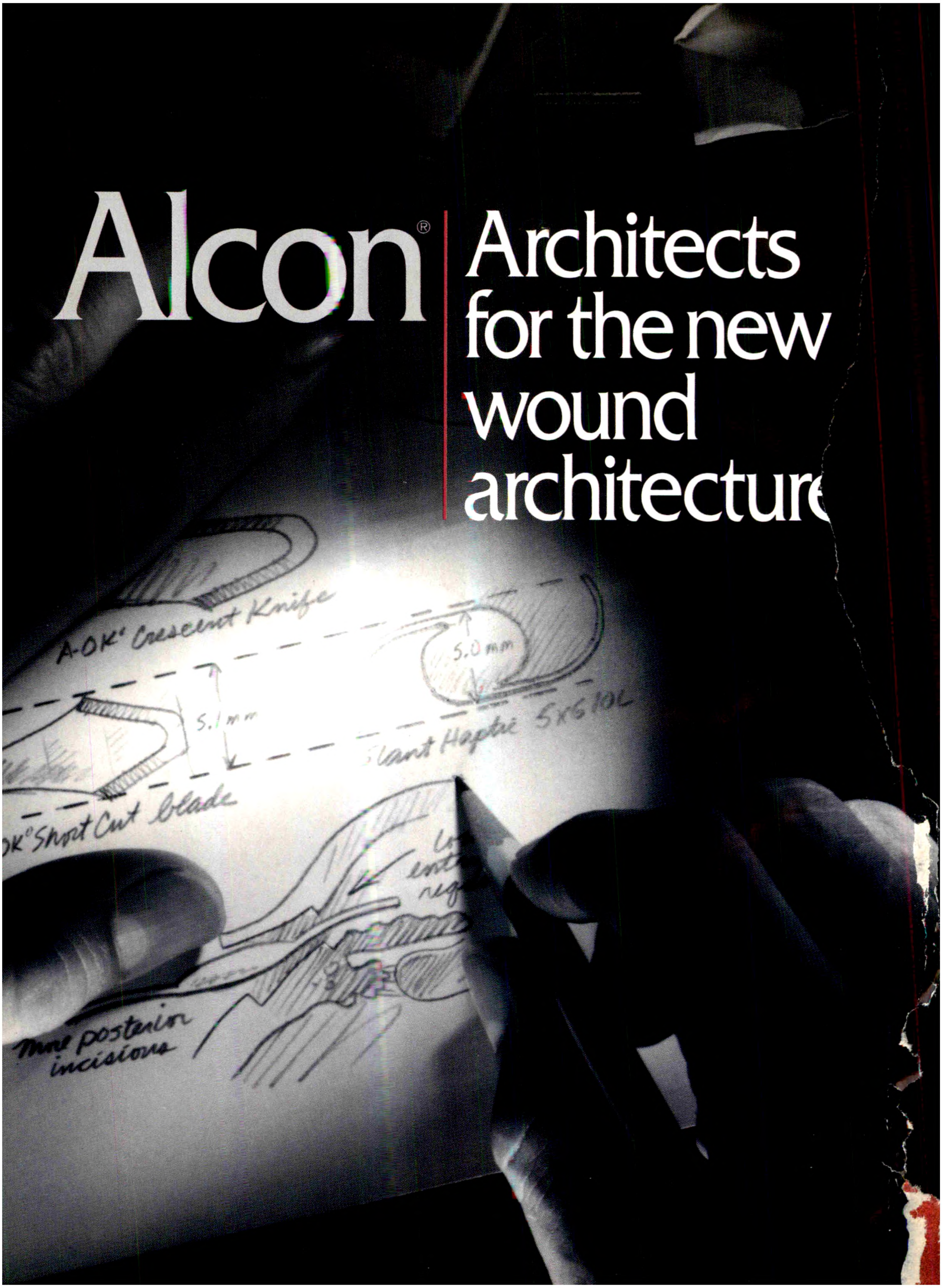
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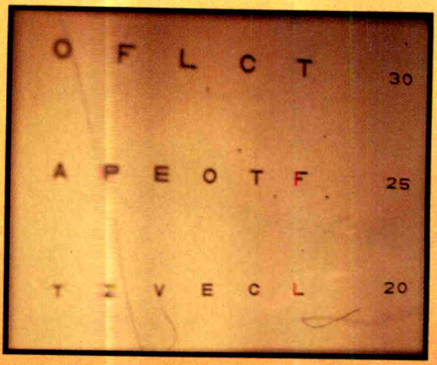

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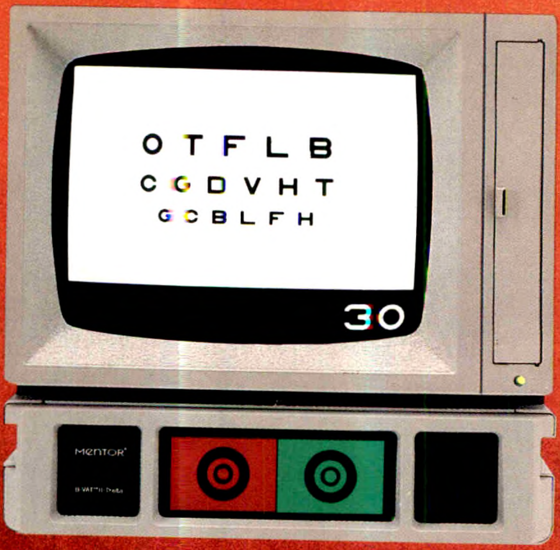

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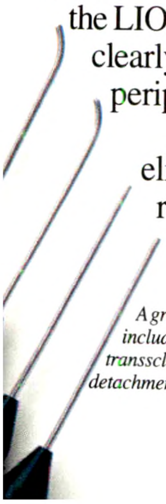

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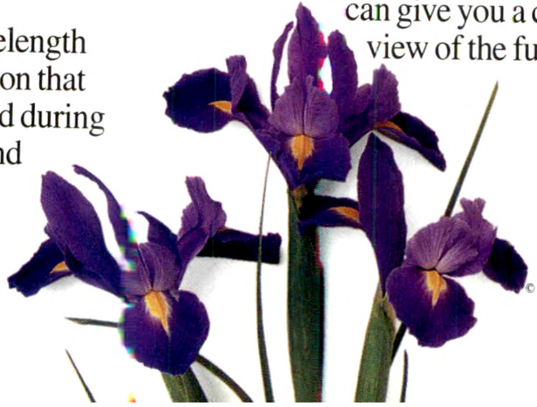

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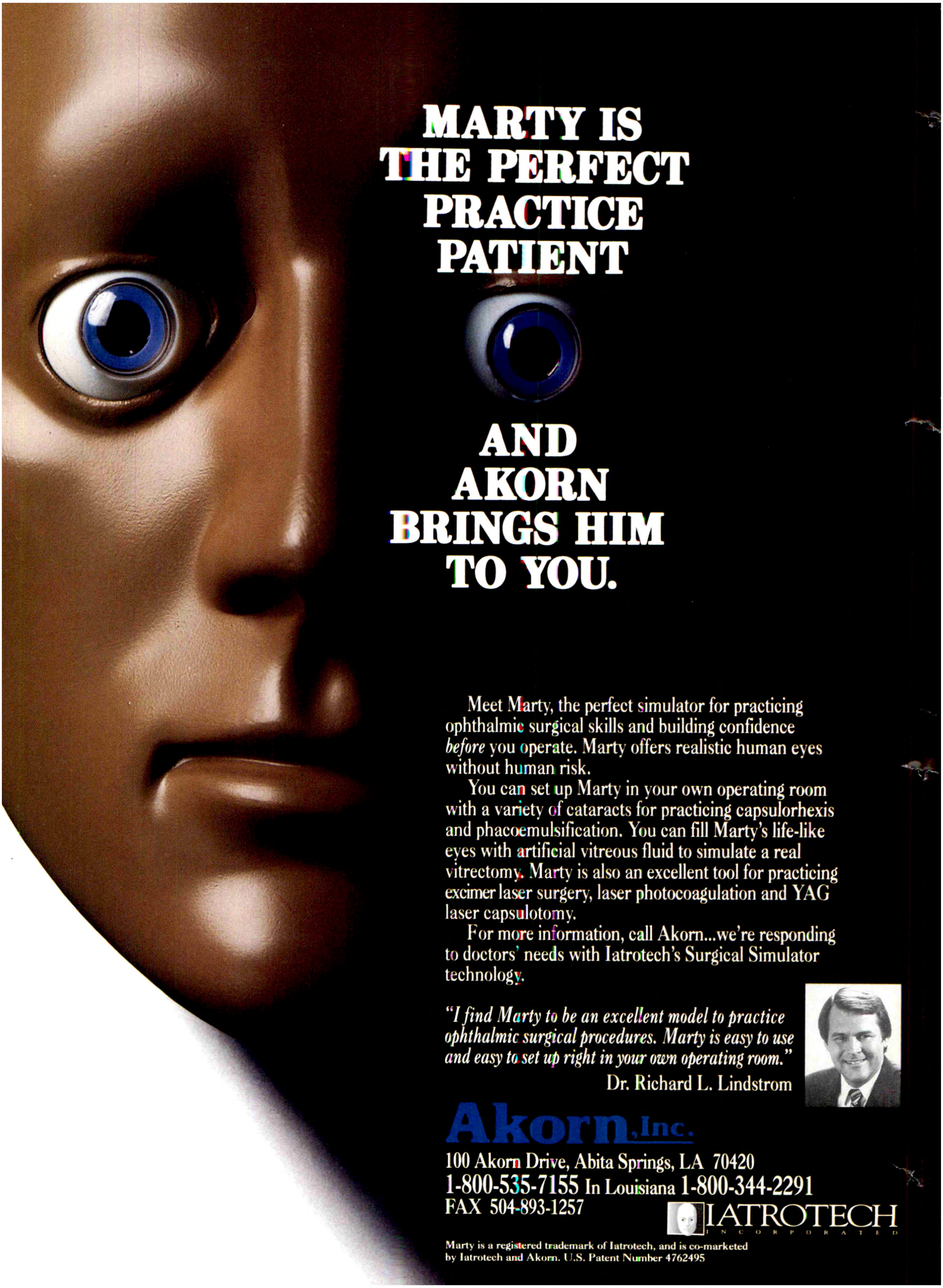

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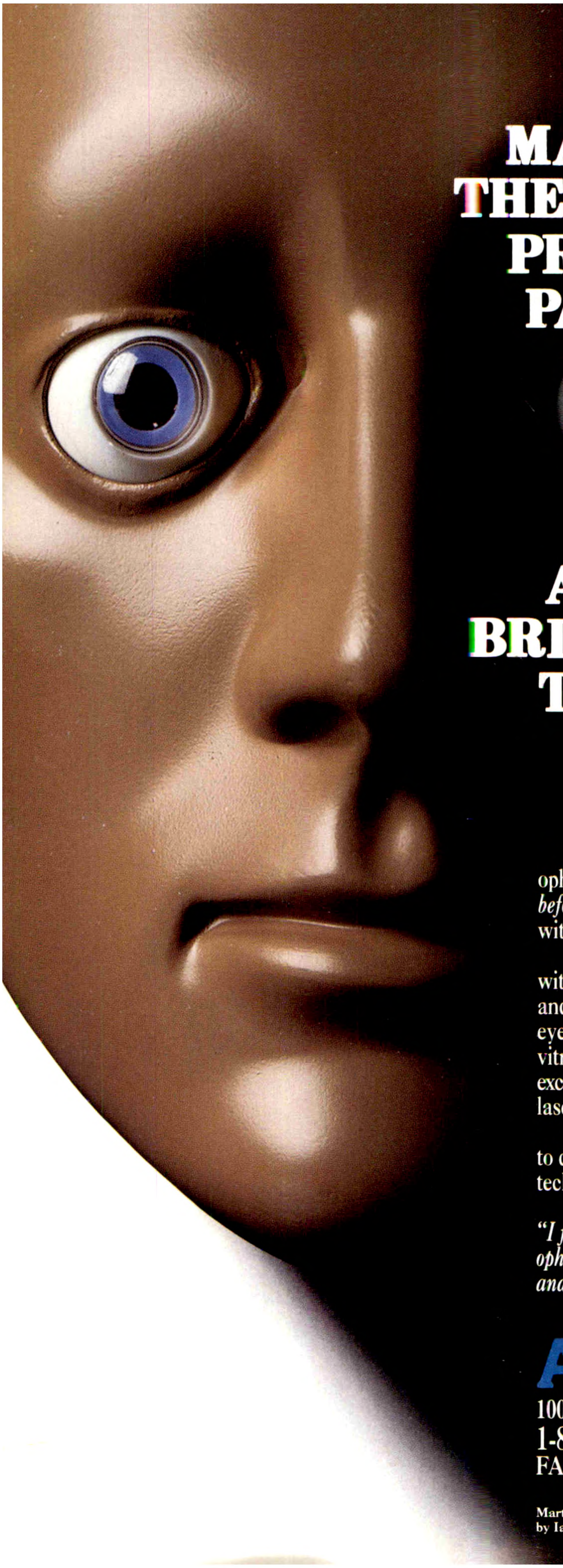

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Cystoid Macular Edema, Retinal Detachment, and Glaucoma After Nd:YAG Laser Posterior Capsulotomy

Roger F. Steinert, M.D., Carmen A. Puliafito, M.D., Sanjiv R. Kumar, M.D., Scott D. Dudak, M.D., and Samir Patel, M.D.

A series of 897 Nd:YAG laser posterior capsulotomies were reviewed for the complications of cystoid macular edema, retinal detachment, new onset of glaucoma, and worsened preexisting glaucoma. After Nd:YAG capsulotomy, 11 patients (1.23%; 95% confidence interval, 0.51% to 1.95%) developed cystoid macular edema and eight patients (0.89%; 95% confidence interval, 0.28% to 1.5%) developed a retinal detachment. The new onset of glaucoma was observed in seven patients (0.78%; 95% confidence interval, 0.20% to 1.36%). Five patients (0.56%; 95% confidence interval, 0.07% to 1.05%) with preexisting glaucoma had persistent worsening of their glaucoma. Most patients with a complication had no identifiable risk factors in common. The numbers of laser pulses and energy delivered were not risk factors. Retinal detachment and cystoid macular edema developed most often many months after capsulotomy and many months to years after the cataract surgery. Patients undergoing Nd:YAG laser capsulotomy therefore require ongoing medical observation to detect and treat these serious complications.

BECAUSE OF ADVANTAGES associated with retention of an intact posterior capsule, including a reduced incidence of cystoid macular edema[1] and retinal detachment,[2] extracapsular cataract extraction has surpassed intracapsular cataract extraction as the standard method of cataract surgery. The most common complication of the extracapsular method is late opacification of the posterior capsule, which has an incidence of 18% to 50%.[3,4]

The management of capsular opacification was greatly simplified by the use of the short pulsed Nd:YAG laser for posterior capsulotomy. Although less invasive and generally considered safer than previous methods of surgical discission, Nd:YAG capsulotomy is associated with several complications. The most common sight-threatening complications after Nd:YAG capsulotomy are cystoid macular edema,[5-1] retinal detachment,[5-15,18-27] and a transient or sustained increase in intraocular pressure.[5-12,14,15,18,28-37] We documented the incidence of new persistent glaucoma, worsened preexisting glaucoma, cystoid macular edema, and retinal detachment after Nd:YAG laser posterior capsulotomy, and assessed potential risk factors for these complications in this study.

Material and Methods

Consecutive Nd:YAG laser posterior capsulotomies performed by 45 physicians at the Massachusetts Eye and Ear Infirmary from 1984 to 1987 were reviewed. The study population comprised the patients treated and monitored by the 41 physicians responding to the survey (response rate, 91%). All capsulotomies were performed using a Q-switched Nd:YAG laser.

Patient information was obtained by a questionnaire to the operating physician, requesting the length of follow-up after YAG capsulotomy, incidence reports for the complications of new glaucoma, worsened preexisting glaucoma, cystoid macular edema, and retinal detachment. Only patients followed up for a minimum of three months were included in this study. Of the 1,116 candidates, 897 patients (80%) met this criterion.

For those patients who had complications, a second and more detailed questionnaire addressing the specific complication was complet-

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Accepted for publication July 3, 1991.

From the Morse Laser Center, Massachusetts Eye and Ear Infirmary, and the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.

Reprint requests to Roger F. Steinert, M.D., Ophthalmic Consultants of Boston, 50 Staniford St., Boston, MA 02114.

ed by the physician. This questionnaire detailed the patient's ophthalmic history, including information on previous cataract surgery, postoperative follow-up, the Nd:YAG procedure, and the complication diagnosis and treatment after Nd:YAG capsulotomy.

Statistical analysis was performed using paired and unpaired two-tailed *t*-tests. For purposes of calculating mean visual acuity, count fingers visual acuity was arbitrarily equated with a Snellen acuity of 20/800.

Results

Thirty-one of the 897 patients (3.46%) developed one or more of the following complications: cystoid macular edema, retinal detachment, new onset of glaucoma, or worsened preexisting glaucoma after Nd:YAG capsulotomy. An intraocular lens had been placed in 22 of the 31 patients at the time of extracapsular cataract extraction. The average time between extracapsular cataract extraction and Nd:YAG capsulotomy for the patients with complications was 23.3 months (range, one to 120 months). An average of 56 laser pulses (range, seven to 200) with a mean energy of 1.8 mJ (range, 0.4 to 4.6 mJ) was used, resulting in a mean total energy of 104.2 mJ (range, 14 to 750 mJ). These 31 patients were monitored for an average of 28.2 months (range, three to 69 months) after capsulotomy.

Cystoid macular edema—Eleven of the 897 patients (1.23%) developed cystoid macular edema after Nd:YAG capsulotomy. Seven of these 11 patients had an intraocular lens placed at the time of extracapsular cataract extraction. Three patients had anterior chamber lenses and four had posterior chamber lenses. None of the patients had loss of vitreous or break of the posterior capsule at the time of extracapsular cataract extraction. The cases involving anterior chamber lenses dated from several surgeons' early extracapsular cataract extraction experience when use of an anterior chamber lens was the surgeon's preference. Postoperative complications had been observed in three patients, consisting of chronic inflammation and an irregular pupil with adhesions in two patients and inflammatory precipitates on the intraocular lens in one patient. Corticosteroids had been used after surgery for an average of 2.4 months (range, one week to six months). Patients were not treated with corticosteroids for an average of 7.5 months (range, zero to 24 months) before capsulotomy. One patient was still being treated with corticosteroids at the time of capsulotomy.

For these 11 patients, the average time between extracapsular cataract extraction and Nd:YAG capsulotomy was 21.9 months (range, two to 120 months). The number of laser pulses used varied from 20 to 200 (mean, 68) with an average energy of 1.5 mJ (range, 0.4 to 2.3 mJ), resulting in a mean total energy of 95.3 mJ (range, 30 to 280 mJ). The time between Nd:YAG capsulotomy and the diagnosis of cystoid macular edema varied from three weeks to 11 months (mean, 4.8 months). The distribution of this time interval is shown in Table 1. A fluorescein angiographic confirmation of cystoid macular edema was obtained for seven of the 11 patients. None of the patients had a history of age-related maculopathy. One patient had a history of diabetic retinopathy. Treatment consisted of corticosteroids for five patients, systemic indomethacin for two patients, and dye-laser macular photocoagulation (577 nm yellow) for the patient with concomitant diabetes.

The distribution of visual acuities of patients developing cystoid macular edema is detailed in Table 2. The visual acuity before Nd:YAG capsulotomy ranged from 20/40 to 20/400 (mean, 20/76). Visual acuities first measured after capsulotomy (ten of 11 patients within six days) but before the diagnosis of cystoid macular edema ranged from 20/20 to 20/100 (mean, 20/37). The last visual acuity recorded at an average follow-up time of 22.3 months (range, three to 45 months) after Nd:YAG capsulotomy varied from 20/25 to counting fingers at six feet (mean, 20/46). The improvement in mean visu-

TABLE 1

DISTRIBUTION OF THE TIME INTERVAL BETWEEN ND:YAG LASER CAPSULOTOMY AND THE DIAGNOSIS OF CYSTOID MACULAR EDEMA OR RETINAL DETACHMENT

MONTHS AFTER CAPSULOTOMY	CYSTOID MACULAR EDEMA	RETINAL DETACHMENT
0-3	5	3
4-6	3	1
7-12	3	1
13-24	0	1
25-36	0	1
37-72	0	1

TABLE 5
VISUAL ACUITY DISTRIBUTION OF PATIENTS WITH NEW ONSET OF GLAUCOMA OR WORSENED PREEXISTING GLAUCOMA AFTER ND:YAG LASER CAPSULOTOMY

	NEW ONSET OF GLAUCOMA (N = 7)		WORSENED GLAUCOMA (N = 5)	
VISUAL ACUITY	BEFORE CAPSULOTOMY	AFTER CAPSULOTOMY	BEFORE CAPSULOTOMY	AFTER CAPSULOTOMY
≥ 20/40	3	6	1	4
20/50-20/60	1	1	2	1
20/70-20/100	2	0	1	0
≤ 20/200	1	0	1	0

formed in the only patient still being treated with topical corticosteroids at the time of capsulotomy. All patients were being treated with one or more glaucoma medications before capsulotomy and required additional glaucoma treatment during the follow-up period, including cyclocryotherapy for one patient.

The average time between extracapsular cataract extraction and Nd:YAG capsulotomy was 22.8 months (range, 15 to 32 months). The number of laser pulses used varied from 30 to 60 (mean, 39) with an average energy of 1.9 mJ (range, 1.6 to 2.4 mJ), resulting in a mean total energy of 72.7 mJ (range, 59 to 102 mJ). The distribution of intraocular pressure is shown in Table 6. The average intraocular pressure before Nd:YAG capsulotomy was 18.8 mm Hg (range, 12 to 24 mm Hg). The highest intraocular pressure measured within a week after capsulotomy occurred at an average of 1.2 days (range, two hours to two days) after the procedure and had a mean value of 30.4 mm Hg (range, 21 to 40 mm Hg). This constituted a mean increase of 11.6 mm Hg (range, 6 to 16 mm Hg), which was statistically significant (P = .003). Mean intraocular pressure at six months after capsulotomy was 24 mm Hg (range, 15 to 38 mm Hg). At last follow-up, an average postcapsulotomy time of 28.4 months (range, 24 to 37 months), the mean intraocular pressure was 19.2 mm Hg (range, 17 to 23 mm Hg).

The visual acuity before Nd:YAG capsulotomy varied from 20/30 to 20/200 (mean, 20/58). Visual acuities measured after capsulotomy varied from 20/25 to 20/50 (mean, 20/32) (Table 5). This improvement in mean visual acuity did not achieve statistical significance (P = .066).

Discussion

This study of 897 Nd:YAG laser posterior capsulotomies by multiple surgeons documents the incidence of the complications of cystoid macular edema, retinal detachment, and persistent glaucomatous changes after this procedure. Previous studies have noted the incidence of cystoid macular edema to be between 0.55% and 4.9% and that of retinal detachments to be between 0.17% and 3.6% (Table 7). In our study, cystoid macular edema had an incidence of 1.23% ± 0.72% (95% confidence interval)

TABLE 6
DISTRIBUTION OF INTRAOCULAR PRESSURE MEASUREMENTS IN PATIENTS WITH WORSENED PREEXISTING GLAUCOMA AFTER ND:YAG LASER CAPSULOTOMY (N = 5)

INTRAOCULAR PRESSURE (MM HG)	BEFORE CAPSULOTOMY	HIGHEST INTRAOCULAR PRESSURE IN FIRST WEEK AFTER CAPSULOTOMY	FOLLOW-UP	
			6 MOS	LAST VISIT
< 15	1	0	0	0
15-19	1	0	2	3
20-24	3	1	1	2
25-29	0	1	1	0
30-34	0	1	0	0
> 34	0	2	1	0

TABLE 7
REPORTED INCIDENCE OF CYSTOID MACULAR EDEMA AND RETINAL DETACHMENT AFTER ND:YAG POSTERIOR CAPSULOTOMY

AUTHOR, YEAR	NO. OF CAPSULOTOMIES	INCIDENCE OF CYSTOID MACULAR EDEMA (%)	INCIDENCE OF RETINAL DETACHMENT (%)
Aron-Rosa, Aron, and Cohn, 1984[8]	3,253	N.A.	0.08
Keates and associates, 1984[9]	526	2.3	0.4
Johnson, Kratz, and Olson, 1984[15]	389	0.8	0.5
Chambless, 1985[7]	210	0.9	0.4
Stark and associates, 1985[14]	2,110*	1.2	0.5
Winslow and Taylor, 1985[13]	1,100	0.55	0.9
Liesegang, Bourne, and Ilstrup, 1985[11]	102	4.9	1.0
Vester and associates, 1986[19]	545	N.A.	1.1
Shah and associates, 1986[5]	2,808	0.68	0.17
Bath and Fankhauser, 1986[12]	3,711	2.5	1.2
Ficker and associates, 1987[24]	582	N.A.	2.0
Ambler and Constable, 1988[25]	862	N.A.	1.4
Rickman-Barger and associates, 1989[26]	366	N.A.	3.6
Dardenne and associates, 1989[27]	1,000	N.A.	1.6
Present study	897	1.23	0.89

*Pooled data; N.A. indicates data not available.

and retinal detachment had an incidence of 0.89% ± 0.61% (95% confidence interval). The precise mechanisms for the development of these retinal complications after Nd:YAG capsulotomy remain unclear. Retention of the posterior capsule in extracapsular cataract extraction has been shown to decrease the incidence of cystoid macular edema and retinal detachment as compared to intracapsular cataract extraction.[1,2] Subsequent investigators generally believe that these complications result from the capsulotomy opening itself and not from factors intrinsically related to the Nd:YAG laser technique.[10,11,13]

Our study included the evaluation of potential risk factors in the development of cystoid macular edema after Nd:YAG capsulotomy. Using pooled data from protocols submitted to the Food and Drug Administration, Stark and associates[14] concluded that the longer the interval between cataract surgery and capsulotomy, the lower the risk of cystoid macular edema. In our study, although the mean time between extracapsular cataract extraction and capsulotomy was 21.9 months for the patients who developed cystoid macular edema, a markedly lower incidence rate for cystoid macular edema was not found, compared to previous reports with shorter surgery to laser intervals. For the 11 patients with cystoid macular edema, corticosteroids were used after surgery for an average of 2.4 months. Three of these patients experienced inflammatory complications after extracapsular cataract extraction. This suggests that these patients may have had a greater inflammatory reaction to their cataract operation than do most cataract patients. The mean interval of 4.8 months between Nd:YAG capsulotomy and diagnosis of cystoid macular edema in this study was longer than the mean interval of two months observed by Winslow and Taylor,[13] but both studies are remarkable for the lag of several months between capsulotomy and the diagnosis of cystoid macular edema. No other predictors were observed in the patients' ocular history. All but one of the patients who developed cystoid macular edema had discontinued postoperative use of corticosteroids before the capsulotomy. Because precapsulotomy fluorescein angiography was not performed, some of these patients may have had ongoing postcataract surgery cystoid macular edema in addition to the capsular opacification. However, in any case, visual acuity worsened after capsulotomy.

Potential risk factors for the development of a retinal detachment were also studied. The number of laser pulses and energy used were similar to those used in other large studies[26,27] for patients who did not develop a retinal detachment and were also similar to the patients in this study developing complications other than retinal detachment. Koch and associates[22] reported myopia to be a risk factor for postcapsulotomy retinal detachment. Only three of our eight patients with a retinal detachment had a history of myopia, however. In a study by Dardenne and associates,[27] more than half of the postcapsulotomy retinal detachments occurred after six months of follow-up. In our study, three of eight patients had a retinal detachment more than one year after capsulotomy. This finding highlights the need for long-term surveillance of patients after this procedure and suggests that the laser energy does not directly cause the detachment.

A transient increase in intraocular pressure after Nd:YAG capsulotomy has been well documented.[5,12,28,29,37] Reports have estimated the incidence of new glaucoma to be between 0.2%[12] and 3%.[14] In our study, the incidence of new glaucoma was found to be 0.78% ± 0.58% (95% confidence interval) and the incidence of worsened preexisting glaucoma to be 0.56% ± 0.49% (95% confidence interval), giving a combined incidence of persistent glaucomatous change of 1.34% ± 0.75% (95% confidence interval). In this study, we could not distinguish between the baseline incidence of new onset glaucoma or naturally progressing glaucoma and any increased rate caused by posterior capsulotomy.

Potential risk factors for the development of immediate increase in intraocular pressure after Nd:YAG capsulotomy suggested in previous studies include the absence of a posterior chamber lens[29,32,37] and the use of higher total energy for capsulotomy.[28] An unidentified vitreous factor has been suggested as the cause of the acute postcapsulotomy increase in intraocular pressure,[37] and a posterior chamber intraocular lens may maintain a vitreous barrier even after posterior capsulotomy. In this study, five of the seven patients with new onset of glaucoma and three of the five patients with worsened preexisting glaucoma had a posterior chamber intraocular lens. This finding indicated that although presence of a posterior chamber implant may result in a lower incidence of transient intraocular pressure increase, such an intraocular lens does not necessarily protect against the onset of persistent increase in intraocular pressure. The mean total energy of 177.2 mJ used for capsulotomy in the patients with new onset of glaucoma was higher than the mean total energy of 72.7 mJ used in the patients with a worsening of glaucoma. However, the difference in this small number of patients did not achieve statistical significance ($P = .44$) and the individual energies used ranged widely. Variables for energy delivered were therefore not predictive risk factors for persistent intraocular pressure increase.

The characteristics of the increase in intraocular pressure were similar for patients with a new onset of glaucoma and for patients with worsened glaucoma. Intraocular pressure increased rapidly after the Nd:YAG capsulotomy and the highest intraocular pressure for the first postcapsulotomy week was recorded within an average of two days for both groups. The mean increase in intraocular pressure was statistically significant ($P = .036$) in the group with preexisting glaucoma, consistent with earlier studies of acute pressure increase.[29]

The Nd:YAG laser is an effective instrument for improving vision hindered by an opacified posterior capsule. Opening of the posterior capsule does, however, carry a low but finite risk of serious complications. Laser capsulotomy is intraocular surgery. Both physician and patient must avoid the false sense of security provided by the high general success rate of laser capsulotomy, because these complications are not uncommon and can be sight-threatening. Clinicians should be alert to the development of cystoid macular edema, retinal detachment, and chronic increase in intraocular pressure during the follow-up of a patient undergoing Nd:YAG posterior capsulotomy.

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References

1. The Miami Study Group: Cystoid macular edema in aphakic and pseudophakic eyes. Am. J. Ophthalmol. 88:45, 1979.

2. Percival, S. P. B., Anand, V., and Das, S. K.: Prevalence of aphakic retinal detachment. Br. J. Ophthalmol. 67:43, 1983.

3. Wilhelmus, K. R., and Emery, J. M.: Posterior capsule opacification following phacoemulsification. Ophthalmic Surg. 11:264, 1980.

4. Sterling, S., and Wood, T. O.: Effect of intraocular lens convexity on posterior capsule opacification. J. Cataract Refract. Surg. 12:655, 1986.

5. Shah, G. R., Gills, J. P., Durham, D. G., and Asmus, W. H.: Three thousand YAG lasers in posterior capsulotomies. An analysis of complications and comparison to polishing and surgical discission. Ophthalmology 17:473, 1986.

6. Harris, W. S., Herman, W. K., and Fagadau, W. R.: Management of the posterior capsule before and after the YAG laser. Trans. Ophthalmol. Soc. U.K. 104:533, 1985.

7. Chambless, W. S.: Neodymium YAG laser posterior capsulotomy results and complications. Am. J. Intraocular Implant Soc. 11:31, 1985.

8. Aron-Rosa, D., Aron, J.-J., and Cohn, H. C.: Use of a pulsed picosecond Nd-YAG laser in 6,664 cases. Am. J. Intraocular Implant Soc. 10:35, 1984.

9. Keates, R. H., Steinert, R. F., Puliafito, C. A., and Maxwell, S. K.: Long term follow-up of Nd-YAG laser posterior capsulotomy. Am. J. Intraocular Implant Soc. 10:164, 1984.

10. Ficker, L. A., and Steele, A. D.: Complications of Nd-YAG laser posterior capsulotomy. Trans. Ophthalmol. Soc. U.K. 104:529, 1985.

11. Liesegang, T. J., Bourne, W. M., and Ilstrup, D. M.: Secondary surgical and neodymium-YAG laser discissions. Am. J. Ophthalmol. 100:510, 1985.

12. Bath, P. E., and Fankhauser, F.: Long-term results of Nd:YAG laser posterior capsulotomy with the Swiss laser. J. Cataract Refract. Surg. 12:150, 1986.

13. Winslow, R. L., and Taylor, B. C.: Retinal complications following YAG capsulotomy. Ophthalmology 92:785, 1985.

14. Stark, W. J., Worthen, D., Holladay, J. T., and Murray, G.: Neodymium:YAG lasers. An FDA report. Ophthalmology 92:209, 1985.

15. Johnson, S., Kratz, R., and Olson, P.: Clinical experience with the Nd:YAG laser. Am. J. Intraocular Implant Soc. 10:452, 1984.

16. Herzeel, M. B., Tassignon, M. J., and Belgrado, G.: Occurrence of cystoid macular edema after Q-switched Nd-YAG laser capsulotomy. Bull. Soc. Belge Ophtalmol. 214:45, 1985.

17. Lewis, H., Singer, T. R., Hanscom, T. A., and Straatsma, B. R.: A prospective study of cystoid macular edema after neodymium:YAG laser posterior capsulotomy. Ophthalmology 94:478, 1987.

18. Terry, A. C., Stark, W. J., Maumenee, A. E., and Fagadau, W.: Neodymium-YAG laser for posterior capsulotomy. Am. J. Ophthalmol. 96:716, 1983.

19. Vester, C. A., Bienfait, M. F., De Jong, P. T., and Pameijer, J. H.: Retinal detachment following neodymium:YAG capsulotomy. Fortschr. Ophthalmol. 83:441, 1986.

20. Leff, S. R., Welch, J. C., and Tasman, W.: Rhegmatogenous retinal detachment after YAG laser posterior capsulotomy. Ophthalmology 94:1222, 1987.

21. Fastenberg, D. M., Schwartz, P. L., and Lin, H. Z.: Retinal detachment following neodymium-YAG laser capsulotomy. Am. J. Ophthalmol. 97:288, 1984.

22. Koch, D. D., Liu, J. F., Gill, E. P., and Parke, D. W.: Axial myopia increases the risk of retinal complications after neodymium-YAG laser posterior capsulotomy. Arch. Ophthalmol. 107:986, 1989.

23. Ober, R. R., Wilkinson, C. P., Fiore, J. V., and Maggiano, J. M.: Rhegmatogenous retinal detachments after Nd-YAG laser capsulotomy in phakic and pseudophakic eyes. Am. J. Ophthalmol. 101:81, 1986.

24. Ficker, L. A., Vickers, S., Capon, M. R. C., Mellerio, J., and Cooling, R. S.: Retinal detachment following Nd:YAG posterior capsulotomy. Eye 1:86, 1987.

25. Ambler, J. S., and Constable, I. J.: Retinal detachment following Nd:YAG capsulotomy. Aust. N.Z. J. Ophthalmol. 16:337, 1988.

26. Rickman-Barger, L., Florine, C. W., Larson, R. S., and Lindstrom, R. L.: Retinal detachment after neodymium:YAG laser posterior capsulotomy. Am. J. Ophthalmol. 107:531, 1989.

27. Dardenne, M. U., Gerten, G. J., Kokkas, K., and Kermani, O.: Retrospective study of retinal detachment following neodymium:YAG laser posterior capsulotomy. J. Cataract Refract. Surg. 15:676, 1989.

28. Channel, M. M., and Beckman, H.: Intraocular pressure changes after neodymium-YAG laser posterior capsulotomy. Arch. Ophthalmol. 102:1024, 1984.

29. Richter, C. U., Arzeno, F., Pappas, H. R., Steinert, R. F., Puliafito, C., and Epstein, C. L.: Intraocular pressure elevation following Nd:YAG laser posterior capsulotomy. Ophthalmology 92:636, 1985.

30. Vine, A. K.: Ocular hypertension following Nd:YAG laser posterior capsulotomy. Ophthalmic Surg. 15:283, 1984.

31. Aron-Rosa, D., Griesman, J.-C., and Arin, J.-J.: Use of a pulsed neodymium YAG laser (picosecond) to open the posterior lens capsule in traumatic cataract. A preliminary report. Ophthalmic Surg. 12:469, 1981.

32. Kraff, M. C., Sanders, D. R., and Lieberman, H. L.: Intraocular pressure and the corneal endothelium after neodymium-YAG laser posterior capsulotomy. Arch. Ophthalmol. 103:511, 1985.

33. Ruderman, J. M., Mitchell, P. G., and Kraff, M.: Pupillary block following Nd:YAG laser capsulotomy. Ophthalmic Surg. 14:418, 1983.

34. Shrader, C. E., Belcher, C. D., Thomas, J. V., and Simmons, R. J.: Acute glaucoma following Nd:YAG laser membranotomy. Ophthalmic Surg. 14:1015, 1983.

35. Parker, M. D., Clorfeine, G. S., and Stocklin, R. D.: Marked intraocular pressure rise following Nd-YAG laser capsulotomy. Ophthalmic Surg. 15:103, 1984.

36. Nirankari, V. S., and Richards, R. D.: Complications associated with the use of the neodymium:YAG laser. Ophthalmology 92:1371, 1985.

37. Schubert, H. D.: Vitreoretinal changes associated with rise in intraocular pressure after Nd:YAG capsulotomy. Ophthalmic Surg. 18:19, 1987.

Treatment of Unilateral Acute Sixth-nerve Palsy With Botulinum Toxin

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We studied 29 consecutive patients with acute unilateral sixth-nerve palsy, who received botulinum toxin injection to the antagonist medial rectus muscle. The average interval between onset of palsy and treatment was 40 days and the mean follow-up from the last injection was 14 months. Before treatment, esotropia in the primary position ranged from 12 to 45 prism diopters and limitation to abduction in the affected eye ranged from −2 (approximately 15 degrees lateral to midline) to −6 (15 degrees nasal to midline). After treatment, 22 of 29 patients (76%) had complete recovery of motility as determined by version testing. Of the seven patients with a residual abduction deficit, two had fusion in the primary position, three had fusion with prismatic correction, and two patients required subsequent surgery. Botulinum toxin injection seems to be an effective treatment option in cases of acute unilateral sixth-nerve palsy.

STUDIES ON THE pharmacologic use of botulinum toxin to weaken extraocular muscles in the treatment of strabismus were first published in 1973.[1] Combined national and international studies provided evidence of both the safety and efficacy of this form of treatment. In 1985, Scott[2] reviewed the available information and indicated conditions in which botulinum toxin injection to an extraocular muscle could be useful. Among the recommended treatments was medial rectus muscle injection in recent sixth-cranial-nerve palsy; it was not recommended for chronic sixth-nerve paralysis.

At our institution, we have used botulinum toxin to treat patients with sixth-nerve palsy during the acute phase. A previous study[3] indicated initial findings in the early postinjection period in a limited number of cases. In this study, we had a longer follow-up and we added a number of patients to the cohort to evaluate further whether this form of treatment is successful in the management of acute sixth-nerve palsy.

Subjects and Methods

From November 1982 through December 1990, 38 patients with a mean age of 55 years (range, 18 to 83 years) had unilateral, acute sixth-nerve palsy at initial examination and all agreed to undergo treatment with botulinum toxin. Five patients were eliminated from the study because of loss of follow-up, two were excluded because of ambiguous diagnosis, and two patients were excluded because treatment took place longer than three months after the onset of the palsy. Twenty-nine patients were included in this study (Table 1).

The interval between onset and botulinum toxin injection ranged from 12 to 90 days (mean, 40 days). Injections of purified botulinum type-A toxin were performed under electromyographic control as previously described by Scott.[2] Doses ranged from 2.5 to 10 units and were determined by the size of the deviation (5 units was the most frequent dose used). The mean follow-up time from the last injection was 14 months (range, five to 51 months).

Deviations were measured, using the prism and alternate cover test at 6 meters and at 0.33 of a meter. Versions were used to assess the range of motility and were graded from 0 (full abduction) to −6, where −4 represents no abduction beyond the midline and −6 indicates abduction that is 15 degrees nasal to midline. Blepharoptosis and vertical deviations secon-

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TABLE 1
CAUSE OF SIXTH-NERVE PALSY

CAUSE	NO. OF PATIENTS
Head trauma	9
Vascular origin in the central nervous system	6
Tumor of the central nervous system	2
Infection in the central nervous system	2
Undetermined	10
Diabetes	0

dary to toxin injection were recorded at each visit. Patients were followed up at two weeks, six weeks, three to four months, and then yearly after injection.

Results

Twenty-nine patients were treated with botulinum toxin injection to the medial rectus muscle in the affected eye (Table 2). Sixteen women and 13 men were in the group. The prevalence of right and left sixth-nerve palsy was essentially equal. Twenty-seven of 29 patients (93%) required only one injection, one patient (3%) received two, and one (3%) underwent three injections.

Before treatment, measurement of the esotropia was 12 to 45 prism diopters, with an average of 32 prism diopters. Limitation to abduction in the affected eye ranged from a minimum of −2 to a maximum of −6.

Of the 29 patients treated, 27 (93%) did not require surgery. Twenty-two (76%) had complete recovery of motility as determined by version testing. All but three of these patients retained single binocular vision with orthophoria in the primary position and sensory fusion. One of the three patients used a small prismatic correction for fusion. One patient had a residual esotropia of 8 prism diopters. Despite full motility, she adopted a small compensatory face turn to alleviate diplopia. The third patient developed a 15-prism diopter left hypertropia after injection, which decreased to 4 prism diopters; he did not notice diplopia.

Of the seven patients with residual limitation to abduction, two required subsequent surgery, three were able to fuse with small amounts of prism, and two patients had sensory fusion in the primary position without prisms.

In those patients requiring prismatic correction, four patients needed only horizontal prisms and two used both horizontal and vertical prisms. In all patients, the correction prescribed was 12 prism diopters or less, split between the two eyes.

After treatment, transient blepharoptosis developed in ten of the 29 patients (34%). A vertical deviation was seen in nine patients (31%) and in all but one, it recovered fully. No instance of permanently induced overcorrection, perforation of the globe, or systemic complication resulting from botulinum toxin injection was observed.

Discussion

After the onset of an acute sixth-nerve palsy, patients are usually observed for a period of six months to allow spontaneous recovery. Serial measurements of the esotropia in primary position along with an evaluation of the paretic muscle's facility of rotation into the field of action serve to indicate whether the palsy is recovering. To alleviate symptomatic diplopia, prism glasses or a patch over one eye may be used temporarily. When diplopia persists after six months, permanent prisms may be used if the deviation is relatively small, but in most cases the patient becomes a candidate for surgery.

Botulinum injection to the antagonist medial rectus muscle in cases of acute sixth-nerve palsy provides a treatment option in the early period after onset and, in most cases, eliminates the need for surgical correction. By pharmacologically denervating the antagonist medial rectus muscle and thus relieving or preventing contracture of that muscle, the resultant balance of forces facilitates recovery of the paretic lateral rectus muscle. As the lateral rectus muscle recovers, a slack medial rectus muscle allows restoration of alignment in the primary position with a marked improvement in abduction. If little or no recovery takes place, subsequent surgery is made easier by the normal length-tension characteristics of the antagonist medial rectus.

In 1985, Scott and Kraft[4] used botulinum toxin to treat a group of patients with lateral rectus muscle palsy. Although some of their

TABLE 2
CHARACTERISTICS OF PATIENTS WITH SIXTH-NERVE PALSY

		BEFORE INJECTION		AFTER INJECTION	
PATIENT NO.	DURATION (DAYS)	DEVIATION (Δ AT 6 M)	ABDUCTION (AFFECTED EYE)	DEVIATION (Δ AT 6 M)	ABDUCTION (AFFECTED EYE)
1	12	20	−2.0	Orthotropia	Full
2	20	38	−2.0	Orthotropia	Full
3	21	16	−4.0	Orthotropia	Full
4	21	25	−4.0	Orthotropia	Full
5	13	30	−2.5	Orthotropia	Full
6	30	45	−4.5	Orthotropia	Full
7	30	45	−4.0	Orthotropia	Full
8	90	30	−4.5	3Δ Esotropia	−1.5
9	60	30	−2.0	2Δ Right hypertropia	Full
10	90	42	−3.0	2Δ Left hypertropia	Full
11	22	15	−4.0	Orthotropia	Full
12	31	26	−1.0	Orthotropia	Full
13	44	40	−4.0	3Δ Esotropia/2Δ Left hypertropia	−1.5
14	30	20	−2.5	Orthotropia	Full
15	30	28	−1.0	Orthotropia	Full
16	47	33	−4.5	Orthotropia	Full
17	75	45	−5.5	Orthotropia	Full
18	60	12	−3.0	Orthotropia	Full
19	60	45	−6.0	12Δ Esotropia	−3.0
20	30	30	−4.0	Orthotropia	Full
21	17	35	−4.0	20Δ Esotropia	−4.0
22	90	45	−6.0	30Δ Esotropia	−4.0
23	35	45	−4.0	Orthotropia	−2.0
24	30	43	−4.0	Orthotropia	Full
25	14	40	−3.5	Orthotropia	Full
26	25	15	−2.0	Orthotropia	Full
27	90	30	−2.0	10Δ Esotropia	−1.0
28	31	45	−4.0	Orthotropia	Full
29	20	16	−2.0	Orthotropia	Full

patients were treated within six months, many were initially injected after the acute stage. In some cases, surgery was avoided. However, when surgery was required, the need for a medial rectus muscle recession was either eliminated or the amount of recession was reduced.

Some patients with acute sixth-nerve palsy will recover spontaneously, particularly those in whom the cause is small-vessel disease.[5] When there is another cause (for example, trauma, stroke, or brain tumor), recovery without treatment is less likely. Metz and Mazow[3] observed spontaneous resolution in only 30% of their patients. In this study, the rate of success for patients treated with botulinum toxin was markedly greater than it was in patients who were monitored only with observation.[3]

Although the benefit of botulinum toxin injection in preventing antagonist muscle contracture has been previously supported,[4] Elston[6] expressed concern about this approach. He indicated that the patient may notice a confusing reversal of diplopia secondary to the transient overcorrection induced by weakening the medial rectus muscle. This was not a problem in our patient population.

Elston and Lee[7] were able to restore binocular sensory and motor function in four patients with acute sixth-nerve palsy who were treated with botulinum toxin. The treatment was considered a safe, effective alternative to surgery and might result in a larger area of single binocular vision compared with the surgical approach.

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In a study of eight patients with intracranial malignancies or vascular lesions who were treated with botulinum toxin injection, Wagner and Frohman[8] found that seven patients had a symptomatic improvement of their diplopia; surgery was avoided in all but one patient. They recommended the use of botulinum toxin injection, especially in patients with sixth-nerve palsy in whom the cause is well documented and the prognosis for spontaneous recovery is poor.

The ability of botulinum toxin to weaken the antagonist medial rectus muscle is unquestioned, but it is not clear how this subsequently promotes recovery of the paretic lateral rectus muscle, because the problem seems to be one originating in the central nervous system. It would be difficult to explain how a peripheral effect of the toxin causes recovery of function of the abducens nerve. In some patients, the deviation may persist secondary to antagonist contracture and this would be expected to be improved by an injection that prevented secondary mechanical changes. However, true lateral rectus muscle recovery does not seem to depend on the strength of the medial rectus muscle, but on the condition of the central nervous system. We cannot explain this outcome although our data could support this conclusion.

Because our study was neither randomized nor prospective, analyzing and interpreting our results are difficult. Additionally, postinjection patient examinations were not performed in a masked fashion. The true rate of spontaneous recovery in acute unilateral sixth-nerve palsy is not certain, and some clinicians believe it to be as high as 70%. Bias can be an issue when the examiner is aware of the type of treatment the patient has received.

Injecting an extraocular muscle with botulinum toxin has some risks. Original concerns about a systemic effect of botulinum toxin have not proven to be of importance.[2] To our knowledge, systemic toxicity in the treatment of strabismus or blepharospasm (in which a larger dose is used) has not been reported. Perforation of the globe has sometimes occurred, and has not been harmful to the patient over time.[2,4] Blepharoptosis and vertical deviation have been observed to develop from 20% to 40% of the time, although these complications have almost always been transitory.[4] Because of the high level of safety and because some patients are able to avoid a surgical procedure, we think that botulinum treatment for patients with acute sixth-nerve palsy may be indicated.

References

1. Scott, A. B., Rosenbaum, A. L., and Collins, C. C.: Pharmacologic weakening of extraocular muscles. Invest Ophthalmol. Vis. Sci. 12:924, 1973.
2. Scott, A. B.: Botulinum toxin therapy of eye muscle disorders. Safety and effectiveness. Ophthalmic procedures assessment recommendations. American Academy of Ophthalmology, 1985.
3. Metz, H. S., and Mazow, M.: Botulinum toxin treatment of acute sixth and third nerve palsy. Graefes Arch. Clin. Exp. Ophthalmol. 226:141, 1988.
4. Scott, A. B., and Kraft, S. P.: Botulinum toxin injection in the management of lateral rectus paresis. Ophthalmology 92:676, 1985.
5. Walsh, F. B., and Hoyt, W. F.: Clinical Neuro-ophthalmology, vol. 1. Baltimore, Williams & Wilkins, 1969, pp. 250–251.
6. Elston, J. S.: Botulinum-A toxin for ocular muscle disorders (letter). Lancet 2:265, 1986.
7. Elston, J. S., and Lee, J. P.: Paralytic strabismus. The role of botulinum toxin. Br. J. Ophthalmol. 69:891, 1985.
8. Wagner, R. S., and Frohman, L. P.: Long-term results. Botulinum for sixth nerve palsy. J. Pediatr. Ophthalmol. Strabismus 26:106, 1989.

The Effects of Lipid Lowering on Diabetic Retinopathy

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The effect of lipid lowering on hard exudates was determined in six consecutive patients with insulin-dependent diabetes mellitus. Diet and hypolipidemic drug therapy including the use of pravastatin, a new inhibitor of 3-hydroxy-3-methylglutaryl coenzyme-A reductase, were used to treat patients for one year. The total cholesterol concentration decreased from a mean baseline value of 231 mg/dl to a treatment mean value of 165 mg/dl. The mean low-density lipoprotein cholesterol concentration decreased from 157 mg/dl to 93 mg/dl. Masked grading of fundus photographs indicated an improvement in hard exudates in all six patients and a decrease in microaneurysms in four patients. Visual acuity improved in one patient and did not change (one line or less change) in five patients. No remarkable side effects resulting from treatment were observed. Our pilot study suggests that aggressive therapy of diabetic patients with hyperlipidemia may have a beneficial effect on background retinopathy.

PATIENTS WITH DIABETES mellitus may have several lipid abnormalities, including increased total cholesterol and triglyceride concentrations.[1,2] The role of dyslipoproteinemia as a cofactor with hyperglycemia, glycosylated proteins, and growth factors in the pathogenesis of diabetic retinopathy is unknown. However, lipid abnormalities can contribute to endothelial damage[3,4] and thereby exacerbate small-vessel disease in the eyes of patients with retinopathy.

Studies during the 1960s attempted to modify the dyslipidemia found in diabetic patients with retinopathy by using a corn oil-enriched diet,[5] clofibrate,[6] or clofibrate in combination with androsterone.[7] Improvement in retinopathy was found. However, the small change in lipid values and the side effects associated with clofibrate therapy have limited the usefulness of these diet and drug therapies.

More potent and safer pharmacologic agents such as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase are now available to control lipids in patients with diabetes. Two such inhibitors, lovastatin[8] and pravastatin,[9] safely and efficiently lower plasma cholesterol concentration in patients with diabetes mellitus.

We studied the effects of diet, pravastatin, and cholestyramine to achieve a targeted mean total cholesterol concentration goal of 150 mg/dl in patients with insulin-dependent diabetes and background retinopathy.

Patients and Methods

Patient population—Seventy patients with diabetes mellitus and a history of hyperlipidemia were screened after a review of the charts of over 1,200 diabetic patients. Six patients who met the inclusion/exclusion criteria were enrolled in the study (Table 1). Patients were included in the study if they had the following: (1) diabetes mellitus of at least five years' duration; (2) insulin therapy for at least three months; (3) hemoglobin A1C concentration less than 7.5% (upper limit of normal, 4.9%) determined by high-pressure liquid chromatography; (4) baseline cholesterol concentration greater than 200 mg/dl and triglyceride concentration less than 300 mg/dl after eight weeks of dietary therapy; and (5) nonproliferative retinopathy with hard exudates in at least one field of the standard seven-field fundus photographs. Patients were excluded from the

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TABLE 1
CHARACTERISTICS OF PATIENTS WITH DIABETES MELLITUS AND RETINOPATHY*

PATIENT NO., GENDER, AGE (YRS)	DURATION OF DIABETES (YRS)	INSULIN THERAPY (YRS)	HISTORY OF HYPERTENSION
1, M, 52	5	5	No
2, M, 35	18	18	No
3, M, 69	14	9	Yes
4, F, 54	13	11	No
5, M, 47	14	5	No
6, M, 43	34	34	Yes

*There was no history of cigarette smoking except in Patient 5 who discontinued smoking approximately one year before study enrollment.

study if any of the following factors applied to them: (1) smoking within six months of enrollment; (2) poorly controlled hypertension; (3) pregnancy; (4) weight more than 20% above ideal despite diet therapy; or (5) laser photocoagulation in the eyes to be evaluated less than one year before enrollment in the study.

Protocol—The protocol was approved by the institutional review board of Cornell University Medical College. This prospective study involved two phases. Throughout the first phase (a baseline period of at least eight weeks), dietary instruction was given and insulin dosage was modified (if necessary).

Throughout the second phase (a one-year treatment period), diet and lipid-lowering drug therapy were used to achieve a mean total cholesterol concentration goal of 150 mg/dl for the study population. All patients were instructed to continue their diet as prescribed throughout the baseline phase and to take 40 mg of pravastatin orally every evening. Lipid and laboratory safety determinations were performed monthly. If the total cholesterol concentration exceeded 170 mg/dl after two months, the patient started to take 8 to 16 g of cholestyramine in divided doses.

Laboratory measurements—Plasma total cholesterol and triglyceride concentrations were determined by enzymatic analysis, using commercial kits (Boehringer Mannheim Biochemicals, Indianapolis, Indiana). The concentration of high-density lipoprotein was measured in plasma after precipitation with dextran sulfate and magnesium chloride.[10] Low-density lipoprotein was determined by calculation, using the Friedewald, Levy, and Frederickson equation.[11] Hemoglobin A1C determinations were performed by SmithKline Beecham Clinical Laboratories (Van Nuys, California), using high-pressure liquid chromatography.

Grading protocol for retinopathy and hard exudates—Visual acuities and standardized seven-field stereoscopic fundus color photographs were taken for each patient before beginning treatment and every three months during treatment. Photographs were taken with a fundus camera by a photographer certified by the Diabetes Control and Complications Trial. The photograph sets were graded for each eye in a masked random fashion, using the Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of diabetic retinopathy.[12] The highest grade in any of the seven standard photographic fields was determined for each lesion, and thus, the retinopathy levels were determined as described by Klein and associates[13] as follows:

Level 10: no retinopathy;
Level 15: retinal hemorrhages only, no microaneurysms;
Level 20: microaneurysms only (one or more);
Level 30: microaneurysms and one or more of the following: retinal hemorrhages and microaneurysms less than standard photograph 2A[14]; hard exudates less than standard photograph 3,[14] soft exudates questionably present; intraretinal microvascular abnormalities questionably present; venous beading questionably present; or small venous loops definitely present[12];
Level 40: microaneurysms and one or more of the following (but definition of level 50 not met): hemorrhages and microaneurysms greater than or equal to standard photograph 2A[14]; hard exudates greater than or equal to standard photograph 3[14]; soft exudates definitely present; intraretinal microvascular abnormalities definitely present; venous beading definitely present; larger venous loops or reduplication definitely present;
Level 50: in fields 4 through 7 only, any three of the following: hemorrhages and microaneurysms greater than or equal to standard photograph 2A in at least one field; soft exudates definitely

present in two fields or more; intraretinal microvascular abnormalities definitely present in two fields or more; venous beading definitely present in two fields or more, or intraretinal microvascular abnormalities present in four fields and greater than or equal to standard photograph 8A[14] in two fields or more;

Level 60: fibrous proliferations only;

Level 61: no evidence of 60 or 65, but scars of photocoagulation either in scattered or confluent patches, presumably directed at new vessels;

Level 65: new vessels on or within 1 disk diameter of the disk graded less than standard photograph 10A[14]; new vessels elsewhere of any extent or preretinal or vitreous hemorrhage, but level-70 definition not met;

Level 70: high-risk characteristics include one or more of the following: new vessels elsewhere greater than 0.5-disk-area in any single photographic field and preretinal hemorrhage or vitreous hemorrhage in any field; new vessels on or within 1-disk-diameter of the disk graded less than standard photograph 10A[14] with preretinal or vitreous hemorrhage, new vessels on or within 1 disk diameter of disk graded greater than or equal to standard photograph 10A[14] with or without preretinal or vitreous hemorrhage[14]; and

Level 80: eyes that could not be graded for retinopathy because of vitreous hemorrhage obscuring the retina, phthisis bulbi, or enucleation secondary to a complication of diabetic retinopathy.

In addition to the level of retinopathy, the severity of hard exudates was graded in fields 2 through 7 as follows[12]: Grade 0, no hard exudates; Grade 1, questionable hard exudates; Grade 2, definite hard exudates present, less than standard photograph 3[14] in one or more fields; Grade 3, definite hard exudates present less than standard photograph 5[14] in one or more fields; and Grade 4, definite hard exudates greater than or equal to standard photograph 5[14] in one or more fields; and Grade 8, could not grade.

The retinopathy in each eye was graded in a masked manner from photographs and ordered by severity of retinopathy from most severe to least severe. The same was done with each set of photographs relative to severity of hard exudates. This process facilitated our evaluation of the trend of the severity of retinopathy and hard exudates during the study.

Results

Side effects from taking 40 mg of pravastatin daily were not remarkable. Liver function test results remained within the normal range in all six patients. Compliance with dietary instruc-

TABLE 2

CHANGES IN LIPID VALUES (MG/DL)*

	TOTAL CHOLESTEROL CONCENTRATION (MG/DL)			LOW-DENSITY LIPOPROTEIN CONCENTRATION (MG/DL)			TRIGLYCERIDE CONCENTRATION (MG/DL)		
PATIENT	BASELINE VALUE	PRAVA-STATIN	STUDY MEAN	BASELINE VALUE	PRAVA-STATIN	STUDY MEAN	BASELINE VALUE	PRAVA-STATIN	STUDY MEAN
1	246	177	184	146	85	91	222	205	216
2	222	175	155	155	113	93	108	86	77
3	216	145	145	150	85	85	172	98	98
4	258	175	174	176	99	95	99	86	89
5	219	164	164	165	105	105	100	108	108
6	226	165	165	152	88	88	133	118	118
Mean	231	167	165	157	96	93	139	117	118

*Total cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations are shown for the diet baseline period the diet and pravastatin alone period (Pravastatin), and for the overall one-year study (Study Mean). Patients 1, 2, and 4 were treated with diet and pravastatin followed by the combination of pravastatin and cholestyramine. Patients 3, 5, and 6 were treated with diet and pravastatin without the addition of cholestyramine to achieve the study lipid goal. Therefore, the pravastatin treatment results are equivalent to the overall study treatment means in Patients 3, 5, and 6.

tion and insulin monitoring was consistent throughout the study and was documented by the mean hemoglobin A1C concentration, which was 6.0% at baseline and 5.9% overall throughout the study. The initial screening (before diet) hemoglobin A1C concentration was 6.4%.

Lipid lowering—Total cholesterol concentration, low-density lipoprotein, and triglyceride concentrations were reduced (Table 2). Administration of 40 mg of pravastatin every evening decreased the mean total cholesterol concentration from a baseline value of 231 mg/dl to 167 mg/dl during the study (28% reduction). This corresponded to a decrease in the low-density lipoprotein concentration from 157 mg/dl to 96 mg/dl (39% reduction). The use of pravastatin reduced the triglyceride concentration 16% (from 139 mg/dl to 117 mg/dl) and increased the high-density lipoprotein concentration by 2 mg/dl. For three of the six patients (Patients 1, 2, and 4) cholestyramine was added to diet and pravastatin therapy when the total cholesterol concentration remained above 170 mg/dl. The addition of cholestyramine reduced the mean total cholesterol an additional 2 mg/dl and low-density lipoprotein cholesterol concentration by 3 mg/dl. Only in Patient 2 was lipid lowering substantially enhanced by the use of cholestyramine.

Ophthalmology—Eleven eyes of six patients could be examined. The eye that was excluded had no light perception. The baseline retinopathy level was 40 in six eyes, 30 in two eyes, and 61 in three eyes. The retinopathy level was unchanged in all eyes at the end of the one-year study. In ten eyes, however, retinopathy improved as assessed by individual variables (Table 3). The individual variables chosen were soft exudates, hemorrhages or microaneurysms, or both, and hard exudates. Of the five eyes that had soft exudates at the beginning of the study, two eyes showed a decrease in soft exudates and three eyes were unchanged. All 11 eyes had hemorrhages or microaneurysms, or both, at baseline; seven of these 11 eyes showed a decrease in this variable, three eyes had no change, and one eye had an increase.

Ten of the 11 examinable eyes had hard exudates at baseline. All ten of these eyes had evidence for improvement in hard exudates during the study (Figure). The hard exudate grade improved by one grade in five eyes. The area of hard exudates diminished in the other five eyes, but not enough to change the hard exudate grade. Hard exudates decreased progressively throughout the one-year study, and improvement was observed usually by six months.

Visual acuity did not change in ten eyes (one line or less change). Visual acuity improved in one eye (Patient 3) from counting fingers at 2

TABLE 3
RETINOPATHY CHANGES

		VISUAL ACUITY		RETINOPATHY LEVEL	HARD-EXUDATE GRADE		CHANGES IN INDIVIDUAL VARIABLES		
PATIENT	EYE	BASELINE VALUE	END OF STUDY VALUE	BASELINE VALUE AND END OF STUDY VALUE	BASELINE VALUE	END OF STUDY VALUE	SOFT EXUDATES	MICROANEURYSMS, HEMORRHAGES	HARD EXUDATES
1	R.E.	20/20	20/25	40	4	3	Decrease	Decrease	Decrease
	L.E.	20/25	20/30	40	4	4	No Change	No Change	Decrease
2	R.E.	20/20	20/20	40	3	2	No Change	Decrease	Decrease
	L.E.	20/15	20/20	40	2	2	No Change	No Change	Decrease
3	R.E.	2 ft*	5 ft*	61	4	4	Not Present	Decrease	Decrease
	L.E.	4 ft*	4 ft*	61	4	4	Not Present	Decrease	Decrease
4	R.E.	20/25	20/25	30	2	1	Not Present	Decrease	Decrease
	L.E.	20/50	20/60	30	1	1	Not Present	Increase	Not Present
5	R.E.	20/20	20/20	40	3	2	Decrease	Decrease	Decrease
	L.E.	20/20	20/20	40	3	2	Not Present	Decrease	Decrease
6	R.E.	20/20	20/20	61	3	3	Not Present	No Change	Decrease
	L.E.	†	†	80	8	8	Not Evaluable	Not Evaluable	Not Evaluable

*The distance at which the patient was able to count fingers.

†No light perception.

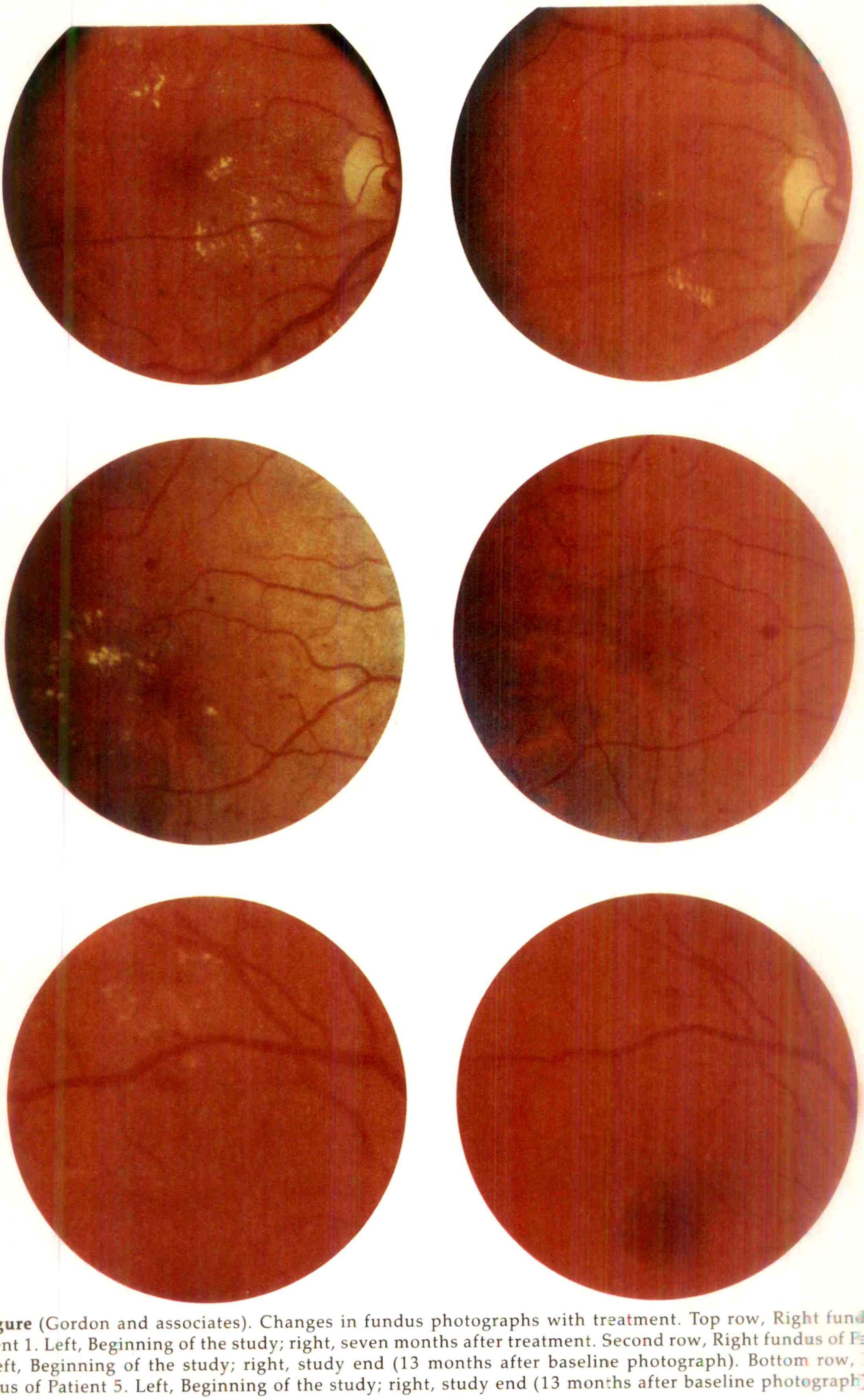

Figure (Gordon and associates). Changes in fundus photographs with treatment. Top row, Right fundus of Patient 1. Left, Beginning of the study; right, seven months after treatment. Second row, Right fundus of Patient 2. Left, Beginning of the study; right, study end (13 months after baseline photograph). Bottom row, Right fundus of Patient 5. Left, Beginning of the study; right, study end (13 months after baseline photograph).

feet to counting fingers at 5 feet. As a result, this patient regained the ability to ambulate independently. New lens opacities were not observed at the end of the study.

Discussion

The results of this pilot study suggest that lipid lowering can improve diabetic retinopathy by reducing hard exudates. To avoid photocoagulation as a confounding variable, none of the patients in the study had undergone laser photocoagulation for diabetic macular edema or neovascular complications for at least one year before enrolling in the study. Patient 3 had completed panretinal photocoagulation for proliferative diabetic retinopathy 12 months before entering the study. Patient 5 had received panretinal photocoagulation ten years earlier and had a failed vitrectomy of the left eye. The severity of hard exudates in the eyes studied varied from those without clinical signs of macular edema, as defined by the Early Treatment Diabetic Retinopathy Study,[12] to extensive exudates and macular edema resulting in loss of ambulatory vision in Patient 3. The reduction of hyperlipidemia in diabetic patients might further enhance reabsorption of hard exudates in patients receiving photocoagulation for clinical signs of macular edema. Hard exudates can also improve spontaneously. Previous studies suggest a rate of approximately 15% to 20% of patients.[6,7] It is unlikely that spontaneous improvement in hard exudates would be seen in ten of ten eyes of six consecutive patients.

The multiple variables that could influence the course of diabetic retinopathy make difficult the demonstration that a single variable such as lipid lowering has an independent effect. Dissecting out the effect of change in glucose control on clinical response is important. The change in blood sugar control alone is unlikely to have caused the beneficial effects in the six patients treated. The mean change in hemoglobin A1C concentration was only 0.4% during the pretreatment dietary phase of the study and 0.1% during the one-year treatment phase. Additionally, in several studies,[15-17] diabetic retinopathy tended to deteriorate rather than stabilize or improve during the first year of improved blood sugar control. Good glucose control may still be necessary for long-term improvement in hard exudates.

Hypertension was not considered an important factor for the improvement in retinopathy because only two of the six patients had any history of hypertension. The two patients with hypertension (Patients 3 and 6) had their blood pressure controlled with medication for several years before entering the study. These two patients continued to have good blood-pressure control during the study.

A beneficial effect of the use pravastatin independent of lipid lowering cannot be ruled out. However, the beneficial effects on retinopathy from other methods of lipid lowering[5-7] suggest a basic relationship between lipid lowering and change in hard exudates.

Our study did not indicate whether a minimal degree of cholesterol concentration lowering or minimal cholesterol concentration was necessary to induce the resulting beneficial effects. The mean total and low-density lipoprotein cholesterol concentrations achieved (165 mg/dl and 93 mg/dl, respectively) were considerably lower than the lipid concentration goals set by the NationalCholesterol Education Program,[18] but consistent with lipid endpoints of two recent studies that induced regression of coronary artery disease.[19,20] Our study suggested that additional potential benefits will result from more intensive lipid lowering in patients with diabetes.

The improvement in retinopathy and hard exudates in our study is encouraging. Controlled and longer studies must be performed before changes in hard exudates can be related definitely to lipid lowering. The effects of lipid lowering on patients receiving focal and grid photocoagulation for diabetic macular edema should also be investigated. In the interim, because of the association of retinopathy with macrovascular disease in patients with diabetes mellitus, every effort should be made to achieve low-density lipoprotein concentrations below the 130 mg/dl concentration goal of the National Cholesterol Education Program.[18]

References

1. Reaven, G. M.: Abnormal lipoprotein metabolism in non-insulin-dependent diabetes mellitus. Am. J. Med. 83:31, 1987.
2. Cruickshanks, K. J., Orchard, T. J., and Becker, D. J.: The cardiovascular risk profile of adolescents with insulin-dependent diabetes mellitus. Diabetes Care 8:118, 1985.
3. Ross, R., and Harker, L.: Hyperlipidemia and

atherosclerosis. Chronic hyperlipidemia initiates and maintains lesions by endothelial cell desquamation and lipid accumulation. Science 193:1094, 1976.

4. Henriksen, T., Evensen, S. A., and Carlander, B.: Injury to human endothelial cells in culture induced by low density lipoproteins. Scand. J. Clin. Lab. Invest. 39:361, 1979.

5. King, R. C., Dobree, J. H., Kok, D'A., Foulds, W. S., and Dangerfield, W. G.: Exudative diabetic retinopathy. Spontaneous changes and effects of a corn oil diet. Br. J. Ophthalmol. 47:666, 1963.

6. Harrold, B. P., Marmion, V. J., and Gough, K. R.: A double-blind controlled trial of clofibrate in the treatment of diabetic retinopathy. Diabetes 18:285, 1969.

7. Duncan, L. J. P., Cullen, J. F., Ireland, J. T., Nolan, J., Clarke, B. F., and Oliver, M. F.: A three-year trial of atromid therapy in exudative diabetic retinopathy. Diabetes 17:458, 1968.

8. Garg, A., and Grundy, S. M.: Lovastatin for lowering cholesterol in non-insulin-dependent diabetes mellitus. N. Engl. J. Med. 318:81, 1988.

9. Yoshino, G., Kazumi, T., Iwai, M., Matsushita, M., Matsuba, K., Uenoyama, R., Iwantani, I., and Baba, S.: Long-term treatment of hypercholesterolemic non-insulin dependent diabetics (NIDDM) with pravastatin (CS-514). Atherosclerosis 75:67, 1989.

10. Warnick, G. R., Benderson, J., and Albers, J. J.: Dextran sulfate-Mg2+ precipitation procedure for quantitation of high density lipoprotein cholesterol. Clin. Chem. 28:1379, 1982.

11. Friedewald, W. T., Levy, R. I., and Fredrickson, D. S.: Estimation of the concentration of low density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. Clin. Chem. 18:499, 1972.

12. Early Treatment Diabetic Retinopathy Study. Manual of Operations. ETDRS Coordinating Center, University of Maryland School of Medicine, Chapter 18. Springfield, Virginia, U.S. Department of Commerce, National Technical Information Service, 1985.

13. Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., and DeMets, D. L.: The Wisconsin Epidemiologic Study of Diabetic Retinopathy VII Diabetic nonproliferative retinal lesions. Ophthalmology 94:1389, 1987.

14. Diabetic Retinopathy Study Research Group: Report 7. A modification of the Airlie House Classification of diabetic retinopathy. Invest. Ophthalmol. Vis. Sci. 21:210, 1981.

15. Lauritzen, T., Prost-Larsen, K., Larsen, H. W., Deckert, T., and The Steno Study Group. Effect of one year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics Lancet 1:22, 1983.

16. The Kroc Collaborative Study Group. Blood glucose control and the evaluation of diabetic retinopathy and albuminuria. N. Engl. J. Med 311:365, 1984.

17. Dahl-Jorgensen, K., Brinchmann-Hansen, O., Hanssen, K. F., Sandvik, L., Aagenaes, O., and The Aker Diabetes Group: Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin-dependent diabetes mellitus. The Oslo Study. Br. Med. J. 290:811, 1985

18. Report of the National Cholesterol Education Program Expert Panel: Detection, evaluation, and treatment of high blood cholesterol in adults. Arch. Intern. Med. 148:36, 1988.

19. Blankenhorn, D. H., Nessim, S. A., Johnson, R. D., Sanmarco, M. E., Azen, S. P., and Cashin-Hemphill, L.: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 257:3233, 1987.

20. Brown, G., Albers, J. J., Fisher, D. L., Schaefer, S. M., Lin, J.-T., Kaplan, C., Zhao, X.-Q., Bisson, B. D., Fitzpatrick, V. F., and Dodge, H. T.: Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N. Engl. J. Med. 323:1289 1990.

Uveitis Precipitated by Nonpenetrating Ocular Trauma

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Although penetrating trauma is a well-recognized cause of uveitis, the role of nonpenetrating trauma in initiating uveitis is not defined. We analyzed the records of 496 patients seen at the uveitis clinic at our institution. Twenty-four of these 496 patients (4.8%) suspected that the cause of their intraocular inflammation was related to previous nonpenetrating trauma. In contrast, only one of 251 patients (0.4%) attending the general ophthalmology clinic for routine care provided a history of recent trauma or attributed the present ocular complaint to trauma ($P < .02$). Patients with posttraumatic uveitis were usually male (19 of 24, 79%), younger (31 ± 16 years) than the average patient examined in the uveitis clinic, and more likely to have unilateral disease. In ten (42%) of the patients the trauma was work-related. Bilateral inflammation was seen in eight (one third) of the patients and 17 of 28 patients (71%) had a considerable degree of inflammation posterior to the lens. Many patients had an identifiable cause of uveitis such as ankylosing spondylitis, Reiter's syndrome, sarcoidosis, or acute retinal necrosis; but most patients had no known predisposition. The role of nonpenetrating trauma in initiating uveitis has implications for diagnosis and treatment.

Penetrating trauma is a well-recognized cause of uveitis in the form of sympathetic ophthalmia.[1] A more common form of uveitis that results from trauma is the self-limited inflammation associated with intraocular surgery such as cataract extraction. Additionally, surgical procedures can markedly exacerbate intraocular inflammation in an eye that has demonstrated previous uveitis.[2]

The role of nonpenetrating trauma in precipitating uveitis is not as well established. Inflammation in other organ systems, however, is frequently triggered by nonpenetrating trauma. Joint inflammation, for example, may be initiated by a contusion[3,4] and skin inflammation may be precipitated by various injuries including sunburn and minor trauma. This latter phenomenon is known as a Koebner reaction and is commonly associated with psoriasis.[5,6] Approximately 25% of patients with psoriasis develop psoriasis in skin subjected to minor irritation.[5]

We analyzed the consecutive records of the uveitis clinic at our institution. Twenty-four of these 496 patients (nearly 5%) attributed their intraocular inflammation to nonpenetrating trauma or had a history of minor trauma usually less than one week before the onset of intraocular inflammation. We analyzed the characteristics of that patient group and compared them to those of the uveitis clinic population as a whole.

Patients and Methods

The characteristics of the uveitis clinic at our institution have been previously described.[7] The patients who are examined are usually referred for additional opinion in regard to diagnosis or treatment. All patients undergo a thorough ophthalmic examination, as well as an examination by an internist or rheumatologist. Our study involved 496 consecutive patients with a diagnosis of uveitis. Patients were examined from Sept. 1, 1985, through July 20, 1990. All patients were seen by one of us (J.T.R.). Charts were reviewed for a history of nonpenetrating trauma that the patient believed to be related to the cause of ocular inflammation.

To compare the prevalence of trauma among patients with uveitis to the prevalence in another patient group, 251 charts representing pa-

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tient visits for routine eye care to the Department of Ophthalmology General Clinic at our institution were reviewed. This control group included 144 patients who wanted a routine refraction or contact-lens examination; 35 patients with an external eye condition such as conjunctivitis; 19 patients with cataract; 18 patients with diabetes; and 35 other patients with miscellaneous conditions including suspected glaucoma, strabismus, macular degeneration, or diplopia. Each physician completed a form that specifically referred to trauma. Patients were excluded if a history related to trauma was not recorded.

Twenty-four of the 496 patients (4.8%) with uveitis attributed their eye disease to previous nonpenetrating trauma. Patients whose uveitis developed after penetrating trauma (for example, those with sympathetic ophthalmia or those with inflammation after insertion of an intraocular lens) were not included among these 24. In the control group, 19 of 251 patients (7.6%) provided a history of recent or remote trauma, but only one of 251 (0.4%) patients in the control group ascribed the current ocular complaint to nonpenetrating trauma. This patient had recurrent corneal erosion. The probability of ophthalmic examination necessitated by nonpenetrating trauma was significantly different between the patients with uveitis and the control group ($P < .02$, by chi-square analysis). Nineteen of the 24 patients with posttraumatic uveitis (79%) were male, whereas only 233 of the 496 patients of the total uveitis clinic population (47%) were male ($P < .01$, by chi-square analysis). Of the 251 control patients, 105 (42%) were male. The average age of patients with posttraumatic uveitis was 31 ± 16 years (mean ± standard deviation), whereas the average age in the uveitis clinic as a whole was 42 years ($P < .01$, by Student's *t*-test). The average age of the control patients in the eye clinic was 43 years. Precipitating trauma included splashes with chemicals; trauma with blunt objects (as with a bat, a tennis ball, or a branch); and pokes, as with a finger. The trauma itself did not usually precipitate ophthalmic examination. In some patients who were being examined years after the onset of uveitis, the duration of time between trauma and the onset of uveitis was difficult to establish; but for most patients, the inflammation usually began within one week of the trauma, and most often within a few days. In ten of the 24 patients (42%), the trauma was related to work. Many patients had a known predisposition to uveitis; two patients had Reiter's syndrome, two patients were HLA-B27 positive, two patients had sarcoidosis, and one patient had ankylosing spondylitis. Of all patients with HLA-B27–associated iritis (patients with Reiter's syndrome, ankylosing spondylitis, or who were HLA-B27 positive, but without joint disease), five of 62 (8%) attributed the eye disease to the trauma. One patient had retinal degeneration and one had suspected interstitial nephritis. One patient developed acute retinal necrosis and a second patient was suspected of having this entity. Sixteen of the 24 patients with posttraumatic uveitis (67%) had unilateral disease, compared with 213 of the 496 patients with uveitis as a whole (43%; $P < .02$, by chi-square analysis). Seventeen of the 24 patients with posttraumatic uveitis (71%) had a marked degree of inflammation posterior to the lens, sometimes involving the choroid or retina. This localization of the inflammation did not differ from that of 496 patients of the uveitis clinic population as a whole, of whom approximately 342 patients (69%) had a marked degree of inflammation posterior to the lens.

Case Reports

Case 1

Hypopyon in an HLA-B27–positive man—An 18-year-old man suffered mild trauma caused by a blunt object to one eye. Five days later, he had a unilateral iridocyclitis in the traumatized eye, associated with the presence of fibrin and hypopyon. The patient had no back or joint complaints, but his family history demonstrated a possibility for ankylosing spondylitis. Endophthalmitis was tentatively diagnosed. However, the patient proved to be HLA-B27 positive and had complete resolution of his inflammation as a result of oral and topical treatment with corticosteroids.

Case 2

Bilateral uveitis in a patient with sarcoidosis—A 14-year-old boy was struck by a tennis ball in the left eye. Vision became blurry in the left eye one to three days later and then became blurry in the right eye two weeks later. Subsequent ophthalmic examination showed the presence of anterior chamber cells, vitreous cells and haze, posterior synechiae, and periphlebitis that was bilateral, but markedly worse in the left eye. Sarcoidosis was diagnosed on the basis of hilar adenopathy, increased angiotensin-converting enzyme concentration in serum, subsequent parotid enlargement, and a skin biopsy showing noncaseating granuloma.

Case 3

Sustained vitreous inflammation—A 37-year-old farm worker developed eye discomfort shortly after being struck by an onion while in the field. Examination four months after the trauma showed a minimal anterior chamber reaction and extensive vitreous cells and debris.

Discussion

Our study indicated that nearly 5% of patients attending a uveitis referral clinic attributed their inflammation to nonpenetrating trauma. Patients with nonpenetrating trauma were more often male, were more likely to have unilateral disease, and were younger than the majority of patients in the uveitis clinic. In general, ocular trauma is most common in a young male population. Surprisingly, one third of the patients had bilateral disease and most patients had considerable inflammation posterior to the lens.

These observations suggest that nonpenetrating trauma may precipitate intraocular inflammation. Several hypotheses could explain this association. In some cases, the inflammation may have preceded the trauma and the trauma merely brought to attention a disease process that had begun insidiously and had therefore been undetected. In other cases, however, the trauma may have had a more causal role. In some instances, an underlying predisposition to inflammation could be identified, but in most cases the inflammation had an idiopathic origin. The process of inflammation has been described as a wound that does not heal. Trauma undoubtedly elicits many of the same mediators such as prostaglandins, cytokines, and growth factors that contribute to inflammation. In contrast to trauma, inflammation involves a positive feedback loop that ordinarily does not terminate without treatment intervention. In a predisposed eye, trauma may initiate this positive feedback loop. Several conditions, the HLA-B27 spectrum of disease, sarcoidosis, and the viral retinitis known as acute retinal necrosis, seem particularly predisposed to being triggered by trauma. We previously observed trauma as a trigger for iritis associated with HLA-B27[8] and trauma has also been observed to initiate HLA-B27–associated joint disease.[3] The relative contribution of trauma in initiating inflammation outside the eye is likewise difficult to ascertain. For example, in rheumatoid arthritis, the role of trauma is debated.[4] At least one study, however, found that 5% of the patients with rheumatoid arthritis had previous trauma,[9] a percentage nearly identical to our observations in regard to uveitis.

Finding bilateral inflammation after nonpenetrating trauma is perplexing and suggests coincidence rather than causality. However, sometimes after vitrectomy we have observed an immediate, self-limited inflammation in the contralateral eye. The early onset and brief duration seem to preclude sympathetic ophthalmia and suggest that inflammation in one eye may trigger contralateral inflammation by an unknown reflex arc.

These observations have potential implications. From a diagnostic perspective, recognition of the syndrome helps to place the inflammation into an etiologic category that may have implications for treatment and prognosis. For example, the history of Case 1 and the recognition that the patient was HLA-B27 positive convinced us to treat the inflammation rather than to perform a vitrectomy for culturing. Our study indicates that many patients experienced the trauma in the work place. Although we do not suggest that nonpenetrating trauma is the only cause of uveitis in these patients (and clearly some of these patients had a predisposing reason to develop uveitis), our observations strongly suggest that nonpenetrating trauma may be a precipitating factor in the development of intraocular inflammation.

References

1. Lubin, J. R., Albert, D. M., and Weinstein, M.: Sixty-five years of sympathetic ophthalmia. Ophthalmology 87:109, 1980.
2. Foster, C. S., Fong, C. P., and Singh, G.: Cataract surgery and intraocular lens implantation in patients with uveitis. Ophthalmology 96:281, 1989.
3. Olivieri, I., Gemignani, G., Christou, C., and Giampiero, P.: Trauma and seronegative spondyloarthropathy. Report of two more cases of peripheral

arthritis precipitated by physical injury. Ann. Rheum. Dis. 48:520, 1989.

4. Wallace, D. J.: The role of stress and trauma in rheumatoid arthritis and systemic lupus erythematosus. Semin. Arthritis Rheum. 16:153, 1987.

5. Farber, E. M., Roth, R. J., Aschheim, E., Eddy, D. D., and Epinette, W. W.: Role of trauma in isomorphic response in psoriasis. Arch. Dermatol. 91:246, 1965.

6. Koebner, H.: Zür aetiologie der psoriasis. Viertelijahresschr. Dermatol. Syphilis 8:559, 1877.

7. Rosenbaum, J. T.: Uveitis. An internist's view. Arch. Intern. Med. 149:1173, 1989.

8. ———: Characterization of uveitis associated with spondyloarthritis. J. Rheumatol. 16:792, 1989.

9. Short, C. L., Bauer, W., and Reynolds, W. E.: Rheumatoid Arthritis. Cambridge, Massachusetts, Harvard University Press, 1957, p. 180.

OPHTHALMIC MINIATURE

But the side of the question that I want to bring before you today . . . is related to what is often called the "diaphragm of the eye," that is, the ciliary body with the suspensory ligaments and capsule. This diaphragm is a great protection to the eye, both from the mechanical escape of vitreous, and also from infection. It powerfully strengthens the anterior hyaloid membrane. That is a matter on which any man with large cataract experience can have no question in his mind. I look upon—and always will look upon—the integrity of the vitreous at the close of a cataract operation as a very great asset.

Col. R. H. Elliot, *Transactions of the International Congress of Ophthalmology*
Washington, 1922, p. 334

Retinal Pigment Epithelial Tears Associated With Trauma

Leonard A. Levin, M.D., Johanna M. Seddon, M.D., and Trexler Topping, M.D.

Two previously healthy patients, a 66-year-old man with blunt trauma to the right eye, and a 28-year-old man with head trauma from a motorcycle accident, were observed to have parafoveal retinal pigment epithelial tears after injury. In both patients, fluorescein angiography demonstrated mottled window defects in the areas of the tears, and blocked fluorescence in the areas of the rolled-up pigment epithelium. Neither eye had evidence of pigment epithelial detachments. We hypothesize that this unusual phenomenon is caused by an acute tractional force oriented tangentially to the macular plane, the result of a rapid spherically expansile deformation of the globe during trauma.

TEARS of the retinal pigment epithelium were first reported in 1981 by Hoskin, Bird, and Sehmi,[1] as a complication of serous detachments of the pigment epithelium in patients with age-related maculopathy. Traction by the raised pigment epithelium at the margin of the detachment may be an important factor in their pathogenesis.[2] Retinal pigment epithelial tears have also been reported in certain other clinical settings, including in patients with a chorioretinal scar,[3] retinal detachments,[3] and after either glaucoma surgery[4] or laser photocoagulation of pigment epithelial detachments[2,5] and subretinal neovascular membranes.[6] We treated two patients with retinal pigment epithelial tears that developed after blunt trauma to the eye.

Case Reports

Case 1

A 66-year-old man was seen in the Emergency Ward one hour after having been kicked in the right eye. There was no loss of consciousness. Except for refractive error, he had no history of previous ocular disorders. On examination, corrected visual acuity was R.E.: 20/100 and L.E.: 20/30, with no improvement with pinhole. The patient had moderate periorbital edema and ecchymosis around the right eye. Examination of the anterior segment of the right eye showed traumatic iritis, with two iris sphincter tears. Mild nuclear sclerosis was present in both eyes. Applanation tension was 21 mm Hg in each eye. The vitreous was clear in both eyes. Ophthalmoscopy of the right eye disclosed an orange-yellow, crescent-shaped area at the level of the pigment epithelium in the fovea, approximately 1 disk diameter in size, with a smaller, concentrically located, pigmented membrane (Fig. 1). A small area of serous detachment of the neuroretina was observed superiorly. There were minimal retinal pigment epithelium changes in the left macula. The peripheral retina was normal in both eyes.

Fluorescein angiography was performed three days later. There was mottled hyperfluorescence of a crescent-shaped area (Fig. 2), corresponding to the depigmented area seen on ophthalmoscopy, which was consistent with a pigment epithelial window defect. There was a smaller area of blocked fluorescence at the inferior edge, projecting into the center of the crescent-shaped window defect, which corresponded to the rolled-up pigment epithelium. Late views demonstrated leakage from a small area at the superior border of the tear (Fig. 3), which outlined the serous retinal detachment on delayed views (Fig. 4). Fluoroangiographic evidence of a pigment epithelial detachment was not seen in either eye.

The patient was seen again one month later. Visual acuity was 20/80 in the right eye. The area corresponding to the depigmented retinal

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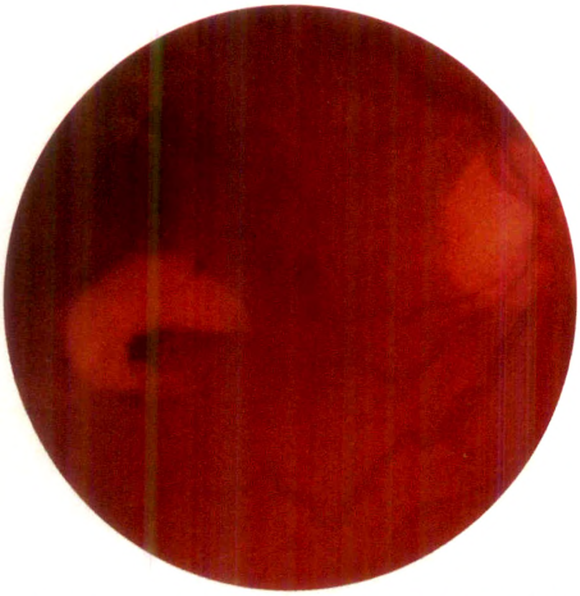

Fig. 1 (Levin, Seddon, and Topping). Case 1. The right eye demonstrated a hypopigmented, crescent-shaped area in the fovea, with a smaller, concentrically located, hyperpigmented membrane, consistent with a retinal pigment epithelial tear. A small serous neuroretinal detachment superiorly was evident on biomicroscopy.

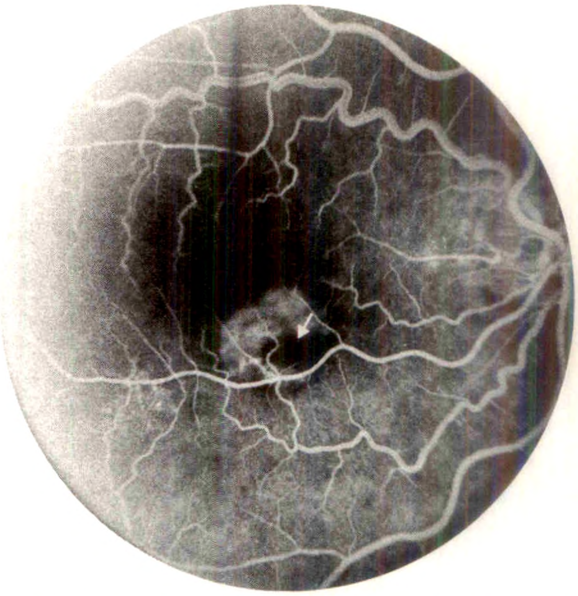

Fig. 2 (Levin, Seddon, and Topping). Case 1. A mid-to-late arteriovenous frame from the fluorescein angiogram demonstrated mottled hyperfluorescence of the crescent-shaped area, consistent with a pigment epithelial window defect, and a smaller area of blocked fluorescence seen inferiorly (arrow), corresponding to the rolled-up pigment epithelium.

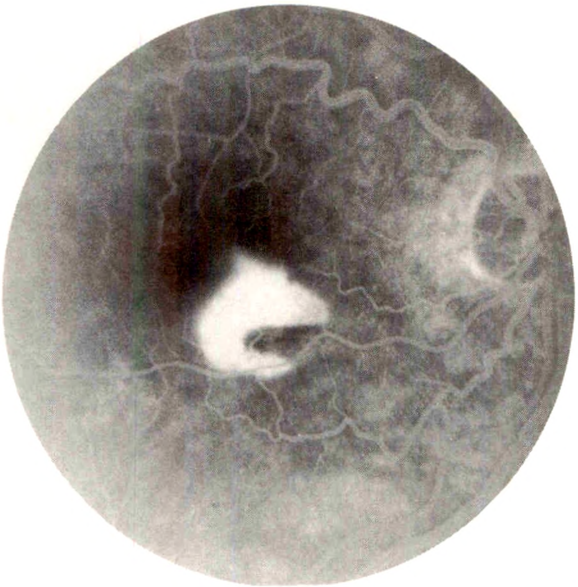

Fig. 3 (Levin, Seddon, and Topping). Case 1. A later frame from the fluorescein angiogram demonstrated beginning leakage from an area at the superior border of the tear.

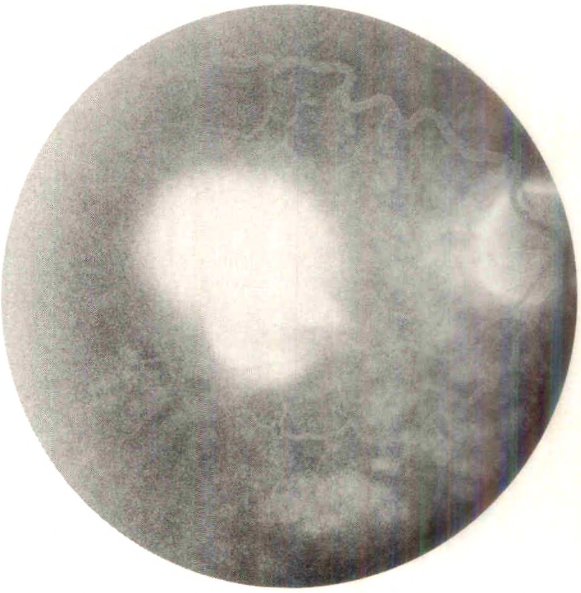

Fig. 4 (Levin, Seddon, and Topping). Case 1. A delayed frame from the fluorescein angiogram demonstrated the extent of the serous retinal detachment superior to the pigment epithelial tear.

pigment epithelial tear remained a mottled orange-yellow. The highly pigmented rolled-up pigment epithelium at the inferior border of the tear had depigmented markedly. On fluorescein angiography, there was still a marked window defect in the area corresponding to the tear, and a persistent late leakage superiorly. The patient was lost to follow-up.

Case 2

A 28-year-old man sustained head trauma and probable chest trauma in a motorcycle accident, losing consciousness for several minutes. He noticed blurred vision in his right eye, and was advised to see an ophthalmologist. There was no history of previous ocular disorders. Upon examination two days later, his visual acuity was R.E.: 20/40, not improving with pinhole, and L.E.: 20/20. Visual fields were full to finger counting in both eyes. The external appearance and anterior segment were normal. The vitreous was clear. Ophthalmoscopy of the right eye (Fig. 5) disclosed a few cotton-wool spots near the optic disk and the papillomacular bundle, consistent with mild Purtscher's retinopathy. Some temporal striae were seen. An orange-yellow, ovoid area approximately 1 disk diameter in size at the level of the pigment epithelium was seen just temporal to the fovea. It was bisected above its midline by a horizontal pigmented band, consistent with a strip of rolled-up pigment epithelium, suggestive of a retinal pigment epithelial tear, with baring of Bruch's membrane. The fovea and peripheral retina appeared normal. The fellow eye was unremarkable.

A fluorescein examination performed the day of clinical examination disclosed a pigment epithelial window defect temporal to the fovea (Fig. 6), corresponding to the retinal pigment epithelial tear that had been seen clinically. There was a narrow horizontal band of blocked fluorescence, corresponding to the rolled-up pigment epithelium. The angiogram also demonstrated some blurring of deeper retinal detail in the areas corresponding to the cotton-wool spots. No leakage was observed in the late phases of the angiogram.

When the patient was seen in follow-up two weeks later, he had symptoms consistent with a

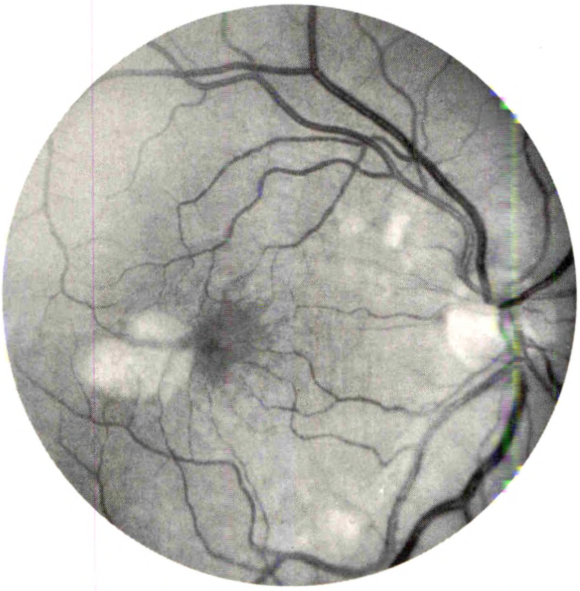

Fig. 5 (Levin, Seddon, and Topping). Case 2. The fundus at initial examination. A hypopigmented ovoid area was seen temporal to the fovea, bisected above the midline by a horizontal hyperpigmented band, consistent with a strip of rolled-up pigment epithelium. A retinal pigment epithelium defect was seen temporal to the tear. Cotton-wool spots were in the nasal macula.

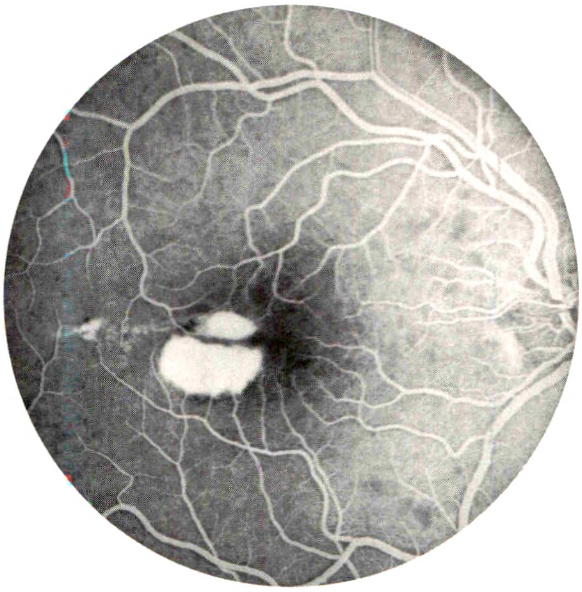

Fig. 6 (Levin, Seddon, and Topping). Case 2. A mid-to-late arteriovenous frame from the initial fluorescein angiogram demonstrated a pigment epithelial window defect temporal to the fovea, corresponding to the area of the retinal pigment epithelial tear. A narrow horizontal band of blocked fluorescence corresponded to the rolled-up pigment epithelium. Window defects were seen temporal to the tear.

right paracentral scotoma. Visual acuity had improved to 20/20 in both eyes. The cotton-wool spots and retinal striae had resolved. The area of pigment epithelial defect temporal to the fovea persisted, but the rolled-up retinal pigment epithelium was smaller and more pigmented. When the patient was seen seven months after the original accident, the findings were the same.

Discussion

Retinal pigment epithelial tears have usually been observed in the presence of pigment epithelial detachments in patients with age-related maculopathy. In these patients, there is tearing at the margin of the detachment, where the raised pigment epithelium meets the flat pigment epithelium. Hoskin, Bird, and Sehmi[1] first described this entity in 1981, presenting data from 44 eyes of 36 patients with retinal pigment epithelial tears. Of these, 12 eyes had been previously examined, and all were observed to have pigment epithelial detachments. Seven patients with retinal pigment epithelial tears that occurred after laser photocoagulation were also described. Because of heterogeneity of the fluorescence pattern seen in the detachments before tearing, these investigators theorized that there were two cleavage planes between pigment epithelium and Bruch's membrane: one between the pigment epithelial basement membrane and Bruch's membrane, and one between the pigment epithelial cells and their own basement membrane. Gass[7] presented evidence to suggest that the only cleavage plane is between the pigment epithelial basement membrane and Bruch's membrane, and that subpigment epithelium choroidal neovascularization was responsible for the detachment and tear. This was consistent with a report by Cantrill, Ramsay, and Knobloch[2] in which six patients with retinal pigment epithelial tears were described. Most of the patients had evidence of occult choroidal neovascularization, presumably as a late result of their age-related maculopathy. These researchers, along with Green and Yarian,[8] also believed that the cleavage plane is between the pigment epithelial basement membrane and the inner collagenous layer of Bruch's membrane, on the basis of the tight adherence of pigment epithelial cells to their basement membrane, as demonstrated by Goldbaum and Madden.[9]

Although retinal pigment epithelial tears were initially described in association with pigment epithelial detachments, in the context of age-related maculopathy, and most reported cases have been consistent with this presumed cause, there have been several other associations.[3,4,7,10] Swanson, Kalina, and Guzak[3] described three cases of retinal pigment epithelial tears that occurred in clinical settings other than pigment epithelial detachments. In a 74-year-old woman, a tear was observed encompassing an old chorioretinal scar, without a known precipitating event. A retinal pigment epithelial tear was seen in association with a rhegmatogenous retinal detachment in a 49-year-old woman with proliferative vitreoretinopathy. A 48-year-old man had a large retinal pigment epithelial tear in the setting of an exudative retinal detachment. Retinal pigment epithelial tears after laser photocoagulation of choroidal neovascular membranes have been described.[6,10] Presumably, tearing is caused by excessive traction from laser-induced shrinkage of the thickened membrane. Laatikainen and Syrdalen[4] described two patients who had retinal pigment epithelial tears after trabeculectomy for open-angle glaucoma. In both patients, hypotony followed the surgery, in association with exudative retinal detachment in one patient, and choroidal detachment in the other.

In each of our cases, there was evidence for significant forces being involved, as shown by the development of traumatic iritis with iris sphincter tears in Case 1, and loss of consciousness and Purtscher's retinopathy (presumably from chest trauma) in Case 2. Although we did not have the opportunity to examine the patients before their trauma, the correlation of a visual defect directly attributable to the retinal pigment epithelial tear (decreased central vision in Case 1 and a paracentral scotoma in Case 2), and a directly observable acute pigment epithelium lesion, suggest that the tears were the result of the trauma. We cannot completely exclude the possibility that the patients had pre-existing pigment epithelial detachments, and that the trauma then precipitated the tearing of the pigment epithelium. However, neither patient had pre-existing metamorphopsia, scotomata, or other visual symptoms. A pigment epithelial detachment would be extremely unlikely in the second patient, a 28-year-old with no other maculopathy.

We therefore believe that the retinal pigment epithelial tears described in these two patients occurred primarily as the result of trauma to the eye. We considered the mechanisms that could underlie this particular response to blunt trauma, and why retinal pigment epithelial tears are so rarely seen in ocular trauma.

We hypothesize that the forces responsible for tearing are a result of acute tangential stresses on and around the posterior pole, similar to those described by Delori, Pomerantzeff, and Cox[11] and Pruett, Weiter, and Goldstein.[12] Trauma only rarely results in retinal pigment epithelial tears, probably because this force must fit into an extremely narrow window. If the force is too strong, both the pigment epithelium and Bruch's membrane will be torn, and the commonly seen choroidal rupture will result. Both choroidal ruptures and retinal pigment epithelial tears have a temporal preponderance.[12,13] If the force is too small, no tears will result. Only if the force is just enough to tear the pigment epithelium, but not Bruch's membrane, will a traumatic retinal pigment epithelial tear result. The tears in our patients were oriented in the horizontal plane, which is an uncommon configuration for choroidal ruptures, but not an impossible one, as shown by Pruett, Weiter, and Goldstein.[12] The horizontal orientation may also reflect differential directional sensitivity to stretch of retinal pigment epithelium and Bruch's membrane. Further observation of similar cases may confirm or disprove this hypothesis.

The more common retinal pigment epithelial tear after pigment epithelium detachment probably results from radial stress on the pigment epithelium when the relatively flexible pigment epithelium and neuroretina are stretched by serous exudate over the far stiffer Bruch's membrane and sclera. Pigment epithelium detachments may be predisposed to tearing, because the window of acceptable forces is significantly wider, and the stretched retinal pigment epithelium can tear with weaker forces. Tearing may occur when the strain exceeds the elastic limits of the tissue. Laser treatment may cause tightening of the pigment epithelium over the detachment, increasing the stress, and thus the risk of a tear.

References

1. Hoskin, A., Bird, A. C., and Sehmi, K.: Tears of detached retinal pigment epithelium. Br. J. Ophthalmol. 65:417, 1981.

2. Cantrill, H. L., Ramsay, R. C., and Knobloch, W. H.: Rips in the pigment epithelium. Arch. Ophthalmol. 101:1074, 1983.

3. Swanson, D. E., Kalina, R. E., and Guzak, S. V.: Tears of the retinal pigment epithelium. Occurrence in retinal detachments and a chorioretinal scar. Retina 4:115, 1984.

4. Laatikainen, L., and Syrdalen, P.: Tearing of retinal pigment epithelium after glaucoma surgery. Graefes Arch. Clin. Exp. Ophthalmol. 225:308, 1987.

5. Norose, K., Tanino, T., and Segawa, K.: Bilateral tears of the retinal pigment epithelium. Br. J. Ophthalmol. 72:621, 1988.

6. Gass, J. D.: Retinal pigment epithelial rip during krypton red laser photocoagulation. Am. J. Ophthalmol. 98:700, 1984.

7. ———: Pathogenesis of tears of the retinal pigment epithelium. Br. J. Ophthalmol. 68:513, 1984.

8. Green, S. N., and Yarian, D.: Acute tear of the retinal pigment epithelium. Retina 3:16, 1983.

9. Goldbaum, M. H., and Madden, K.: A new perspective on Bruch's membrane and the retinal pigment epithelium. Br. J. Ophthalmol. 66:17, 1982.

10. Yeo, J. H., Marcus, S., and Murphy, R. P.: Retinal pigment epithelial tears. Patterns and prognosis. Ophthalmology 95:8, 1988.

11. Delori, F., Pomerantzeff, O., and Cox, M. S.: Deformation of the globe under high-speed impact. Its relation to contusion injuries. Invest. Ophthalmol. 8:290, 1969.

12. Pruett, R. C., Weiter, J. J., and Goldstein, R. B.: Myopic cracks, angioid streaks, and traumatic tears in Bruch's membrane. Am. J. Ophthalmol. 103:537, 1987.

13. Decker, W. L., Sanborn, G. E., Ridley, M., Annesley, W. H., and Sorr, E. M.: Retinal pigment epithelial tears. Ophthalmology 90:507, 1983.

Management of the Dislocated Crystalline Lens With a Perfluorocarbon Liquid

Michael J. Shapiro, M.D., Kenneth I. Resnick, M.D., Sang H. Kim, M.D., and Aaron Weinberg, M.D.

Vitreoretinal surgery allows the effective removal of soft to moderately dense crystalline lens fragments, using the vitrectomy probe and the ultrasonic fragmentation probe. Hard lenses cannot be removed with these instruments. Previously described techniques for removal of hard lenses include trapping the lens anteriorly with needles, cryoextraction of the lens in an air-filled eye, and manipulation with sodium hyaluronate. These methods are difficult and dangerous in some cases. We used perfluorocarbon liquid to facilitate the safe removal of a surgically luxated hard crystalline lens. Injection of the perfluorocarbon liquid floated the lens off the retinal surface and into the anterior vitreous cavity. In this location, the lens was delivered by using standard extracapsular cataract extraction techniques. This technique allowed removal of the hard crystalline lens with minimal manipulation, and was helpful in the setting of poor media clarity.

DISLOCATION OF THE crystalline lens during cataract surgery often leads to severe uveitis, glaucoma, and vitreous condensation. If untreated, vision may be permanently lost.[1] Treatment of dislocated lenses and lens fragments has improved with the advance in vitrectomy techniques. Soft to moderately hard lenses are safely treated with the vitrectomy probe, ultrasonic fragmentation probe, and microvitreous forceps.[2-4] Nonetheless, removal of hard lenses remains hazardous. Several techniques prone to failure and complication have been reported. They include posterior cryoextraction in an air-filled eye,[3,5] double-needle trapping after placing the patient in a face-down position,[6] and sodium hyaluronate manipulation of the hard lens into the anterior vitreous cavity.[7] We used a technique that employed the special properties of perfluorocarbon liquids to facilitate the safe removal of a hard crystalline lens from the retinal surface. Moreover, we successfully applied this technique in a difficult and dangerous situation, an eye with partial corneal opacification and poor view of the retinal detail.

Case Report

A 75-year-old man was referred because of a dislocated crystalline lens one day after cataract surgery in the right eye. Fifty years earlier he had suffered a corneal chemical burn of the right eye. Visual acuity was hand motion in the right eye and 20/40 in the left eye. Examination of the right eye disclosed a superior limbal incision with intact sutures. The superior cornea had a pannus extending 2.5 mm over the cornea. Additionally, two opaque scars were in the superior nasal paracentral area. The corneal epithelium and stroma were edematous, with severe striae of Descemet's membrane. Intraocular pressure as determined by Goldmann applanation was 47 mm Hg. Although the view of the anterior chamber was poor, lens remnants could be seen in the pupil. No fundus detail was visible with indirect ophthalmoscopy. Examination of the left eye disclosed a well-positioned, posterior chamber intraocular lens in an otherwise healthy eye.

Informed consent was obtained from the patient. Because of the superior pannus, the surgical approach was from the temporal aspect of the eye. A 6-mm infusion cannula was placed at

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the 2:00 o'clock position and the other sclerotomies were made at the 10:00 and 8:00 o'clock positions. The vitreous probe was brought into the eye, and the central cortical lens remnants and anterior vitreous gel were removed. The peripheral rim of vitreous gel, lens cortex, and capsule were removed using scleral depression. After the vitrectomy was completed, the nucleus with parts of the cortex was found resting on the retina. At this time, a silicone-tipped cannula was brought into the eye and perfluoro-octane was injected. The lens was lifted off the retina (Fig. 1). Additional injection of perfluoro-octane liquid enlarged the globule and floated the lens anteriorly. The lens was partially wedged between the globule and the inferior ciliary body (Fig. 2). Brushing with the soft-tipped cannula against the lens moved it centrally behind the pupil (Fig. 3). Visualization was inadequate to attempt ultrasonic fragmentation. Therefore, a temporal corneal limbal incision was made. The lens was delivered with a lens loop under gentle pressure from the balanced saline (0.64% NaCl) solution infusion (Fig. 4). After closing the limbal incision, the endoilluminator and silicone-tipped extrusion needle were brought into the eye, and the perfluoro-octane was removed. The lens specimen was brunescent.

After surgery, the retina remained attached. The pressures declined to 20 mm Hg without treatment. The cornea had a mild bullous keratopathy, and postoperatively the uncorrected improvement in visual acuity improved to 3/200.

Discussion

Vitreous surgery for removal of dislocated crystalline lenses is usually performed when severe inflammation and glaucoma are present. Commonly, this glaucoma is phacolytic. Typical phacolytic glaucoma was observed and reported in the leaking hypermature lens. The release of soluble lens proteins induced a phagocytic response. The free protein and the macrophages distended with protein, blocked the trabecular meshwork outflow, and caused the intraocular pressure to increase. In cases of frank capsule rupture, the early pressure increase from residual cortex is caused by the soluble proteins with little contribution from macrophages. Therefore, the term lens particle glaucoma has been applied. If untreated, lens-induced inflammation may also induce a persistent glaucoma caused by peripheral anterior synechiae, a dense pupillary membrane, vitreous opacification, cystoid macular edema, and retinal detachment.[1] Additionally, corneal manipulation is often increased in cases of surgical dislocation, frequently resulting in endothelial injury. Therefore, patients commonly have inflammation, glaucoma, vitreous opacification, and bullous keratopathy at initial examination. The poor outcome of untreated eyes and the complexity of the problems at initial examination make the management of the surgically dislocated crystalline lens both imperative and challenging.

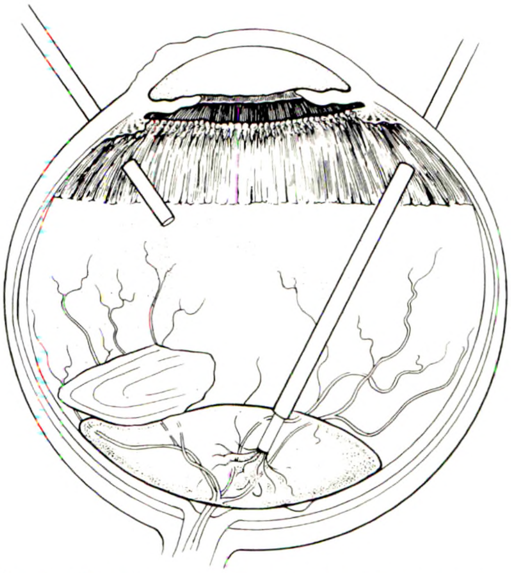

Fig. 1 (Shapiro and associates). Cross-sectional illustration of the operative situation after removal of the anterior cortical lens remnants and the vitreous gel, showing the liquid perfluorocarbon floating the lens off the retinal surface during injection above the optic nerve.

Many techniques have been described for the removal of dislocated crystalline lenses. The critical factors that determine the surgical approach include the amount of lens material, extent of dislocation, degree of mobility, density of the lens, and media clarity. Accompanying factors including retinal detachment, vitreous incarceration, and iris trauma must also be considered before and during surgery.

Small amounts of lens material are common-

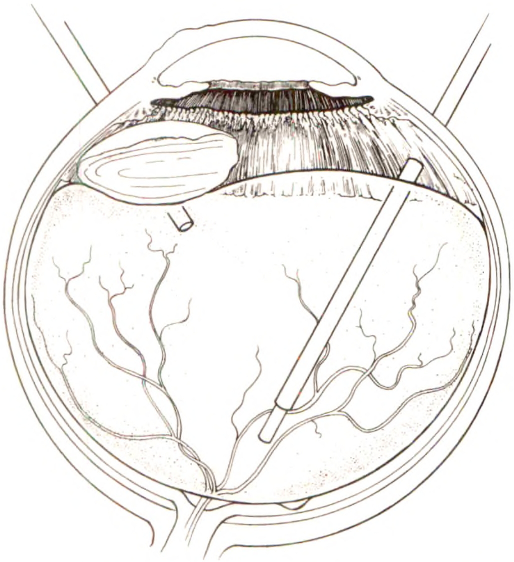

Fig. 2 (Shapiro and associates). Intraoperative illustration showing the globule wedging the lens under the iris.

ly found in many postoperative eyes. They appear to be well tolerated within the capsule. Small fragments are often tolerated posteriorly as well. In these cases, medical treatment of inflammation and glaucoma often allows resorption of the residual material without surgery. Larger lens fragments and multiple lens fragments often are not medically manageable and require surgical removal. Dislocated lenses with intact capsules may be left undisturbed until complications develop. Small fragments are removed with the vitreous probe and ultrasonic fragmentation probe.[2-4] The technique for removal of large fragments and whole lenses depends on location, hardness, and media clarity.

Mobile lens fragments from either subluxated or luxated lenses may be coaxed into the anterior chamber or vitreous cavity by placing the patient in a face-down position during surgery. The patient is retained in a face-down position until the lens is seen in the anterior chamber or vitreous cavity. Specially developed needles are then passed across the eye at the level of the pars plana. The patient is then rotated to a supine position and the lens is removed. This technique may be applied to hard as well as soft lenses. The disadvantages of this method include its limitation to mobile lenses, logistic difficulty with patient rotation and maintenance of the sterile field, and blind passage of dangerous instruments through the eye in an inconvenient position. Serious complications have been reported.[6] Residual zonular attachments may also hold subluxated lenses anteriorly. After the vitreous connections are cleared from the lens, the surgeon may choose a pars plana or anterior approach on the basis of the density of the lens.

Soft to moderately dense crystalline lenses are commonly removed with the vitrectomy probe and ultrasonic fragmentation probe. In cases of moderately dense lenses for which ultrasound power is inadequate, a crush technique may help. This is a bimanual technique by which the lens is mechanically crushed between the endoilluminator and the ultrasonic fragmentation probe or vitrectomy probe. Typically, the moderately dense lens is lifted into the center of the vitreous cavity, using aspiration. It is fragmented or crushed and the remaining fragments fall back onto the retina. This process is repeated many times until the fragments can be aspirated.[2,3] The retina can be traumatized during this procedure from the falling lens fragments, from the high energy of the ultrasonic fragmentation probe, or even from the vitreous probe. Eventually, all the lens material may be removed.

Ultrasonic fragmentation and the crush technique are ineffective and dangerous for hard

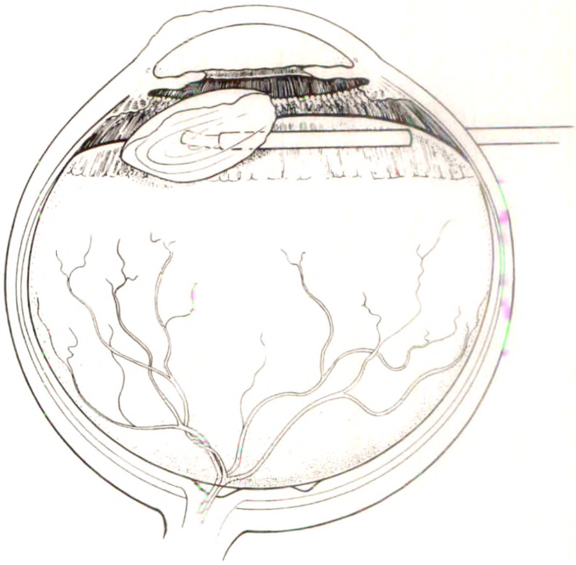

Fig. 3 (Shapiro and associates). Intraoperative illustration showing manipulation of the lens from under the iris, using a brushing movement with a flexible silicone-tipped extrusion needle.

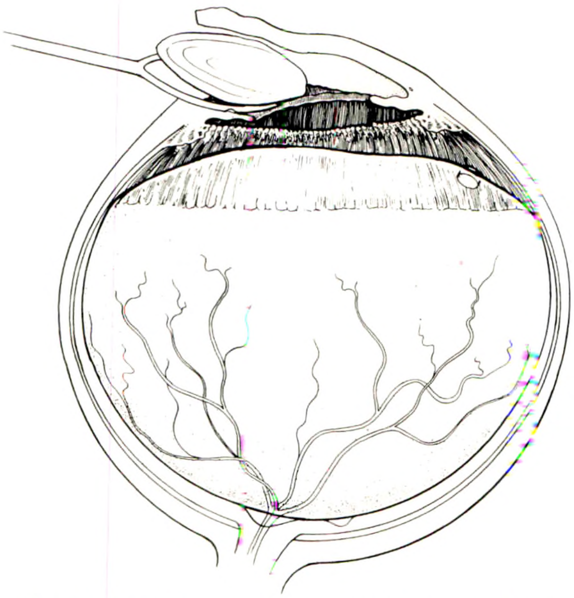

Fig. 4 (Shapiro and associates). Intraoperative illustration showing the lens being removed using a lens loop and gentle pressure from the 0.64% balanced saline solution infusion.

lenses. The hard lens requires elevation into the anterior chamber and removal through a limbal or corneal wound. Techniques have been described for removal of the poorly mobile posterior luxated lens. Use of a cryoprobe in an air-filled eye[3] requires excellent visibility in order to monitor the position of the probe and the iceball. Misapplication of the probe becomes a concern at the time of engaging the lens on the retina, as well as during anterior manipulation of the enlarging iceball to the corneoscleral limbus. Initial visibility is poor in many cases and the view is further impaired when the eye is filled with air. Although the problem of corneal opacity may be resolved using a cryoprobe in an open-sky approach,[5] this surgery is complicated by new visibility problems common in open-sky vitrectomy. Therefore, misapplication of the probe remains a considerable risk. Use of sodium hyaluronate has been reported and is much less hazardous than the previous techniques.[7] The sodium hyaluronate is carefully injected under the lens in order to buoy it up. This technique requires clear media to direct the viscous material correctly and remove the sodium hyaluronate safely. Because the infusion must be off during injection of the viscous material, the eye may become hypotonous and miosis will sometimes result. Additionally, the sodium hyaluronate may also induce glaucoma. All the techniques described for removal of the poorly mobile hard lens require clear visualization of the lens and retina. Most of the techniques are hazardous or prone to failure because of the surgical complexity. The mild corneal scarring and opacification as we found in our case would require the addition of an open-sky approach or keratoprosthesis with pars plana approach to already difficult methods of lens removal.

Because of their density, inert behavior, and low viscosity, liquid perfluorocarbons have been used for the attachment of giant retinal tears and other retinal detachments.[8,9] These same properties allow safe removal of hard lenses from eyes with suboptimal visualization. The crystalline lens is floated off the retina with minimal instrumentation. This allows the lens to be brought safely into the anterior vitreous cavity. In this location, the lens can be removed through the anterior chamber. Our concern for mechanical abrasion of the corneal endothelium with the heavy perfluorocarbon liquid motivated us to minimize its contact with the cornea. Therefore, we used gentle pressure from the balanced saline (0.64% NaCl) solution infusion and manually delivered it with a lens loop rather than expel the lens by increasing the perfluorocarbon globule into the anterior chamber. After closing the limbal wound, the liquid perfluorocarbon is easily removed. Its relatively high density causes it to pool posteriorly at the optic nerve and its low viscosity allows the use of a small-gauge extrusion needle. We found that this method greatly simplifies the removal of dislocated hard lenses and is preferable to the available alternative techniques.

References

1. Epstein, D. L.: Chandler and Grant's Glaucoma, ed. 3. Philadelphia, Lea & Febiger, 1986, pp. 320–331.

2. Hutton, W. L., Snyder, W. B., and Vaiser, A.: Management of surgically dislocated intravitreal lens fragments by pars plana vitrectomy. Ophthalmology 85:176, 1978.

3. Charles, S.: Vitreous Microsurgery, ed. 2. Baltimore, Williams & Wilkins, 1987, pp. 48–51.

4. Peyman, G. A., and Schulman, J. A.: Intravitreal Surgery. Principles and Practice. East Norwalk, Connecticut, Appleton-Century-Crofts, 1986, pp. 126–130.

5. Barraquer, J.: Surgery of the dislocated lens. Trans. Am. Acad. Ophthalmol. Otolaryngol. 76:44, 1975.

6. Calhoun, F. P., and Hagler, W. S.: Experience with José Barraquer method of extracting a dislocated lens. Am. J. Ophthalmol. 50:701, 1960.

7. Haymet, B. T.: Removal of a dislocated hypermature lens from the posterior vitreous. Aust. N.Z. J. Ophthalmol. 18:103, 1990.

8. Chang, S., Lincoff, H., Zimmerman, N. J., and Fuchs, W.: Giant retinal tears. Surgical techniques and results using perfluorocarbon liquids. Arch. Ophthalmol. 107:761, 1989.

9. Chang, S., Reucci, V., Zimmerman, N. J., Heinemann, M., and Coleman, D. J.: Perfluorocarbon liquids in the management of traumatic retinal detachments. Ophthalmology 96:785, 1989.

OPHTHALMIC MINIATURE

I had pictures painted on the walls of the waiting room. In one of these Imhotep the Wise, the god of doctors, was shown giving me instruction. I was painted small before him, as the custom is, but below the picture was an inscription that ran thus:

Wisest and most skillful of thy disciples
is Sinuhe, Son of Senmut, He Who Is Alone.

Another picture showed me making sacrifice to Ammon, that I might be seen to do him honor and win the confidence of my patients. But in a third, great Pharaoh looked down upon me from the heavens in the shape of a bird, while his servants weighed out gold for me and clothed me in new robes.

Mika Waltari, *The Egyptian*
Helsinki, WSOY, 1983, p. 65

Familial Congenital Grouped Pigmentation of the Retina

Victor W. Renardel de Lavalette, M.D., Johan R. M. Cruysberg, M.D., and August F. Deutman, M.D.

Congenital grouped pigmentation of the retina is an uncommon disorder characterized by a grouping together of round to oval spots of pigment in one or more quadrants of the retina, except for the macula. Detection is usually coincidental during routine ocular examination. We examined a mother and daughter with bilateral grouped pigmentation of the retina. Visual acuity, visual fields, and results of electrophysiologic examination were normal. Autosomal dominant inheritance with variable expression was likely.

CONGENITAL GROUPED PIGMENTATION of the retina is an uncommon ophthalmoscopic finding. The first case was encountered by Mauthner[1] in 1868. Several reports appeared in the following years, but it was not until 1911 that Hoeg[2] used the name "grouped pigmentation of the retina" in a review of the literature to which he added four cases that he had seen in seven years of practice. The condition is known by the following names: melanosis retinae, congenital pigmentary plaques of the retina, congenital pigmentation of the retina, nevoid pigmentation of the fundus, and bear or animal tracks.[3-6] Except for the conclusions of two recent studies that suggest otherwise,[7,8] grouped pigmentation has always been considered sporadic in frequency.

We examined a mother and daughter who had typical grouped pigmentation of the retina.

Case Reports

A 3-year-old girl was seen in our outpatient department because of possible strabismus. On examination the visual acuity in both eyes was 20/20 without correction. Strabismus was not evident. The anterior segments and media were clear. Ophthalmoscopy showed normal macular reflexes, normal optic disks and vessels, but extensive areas of well-delineated, flat, dark-gray pigmented spots in all quadrants of both eyes (Fig. 1). The round to oval spots were grouped in clumps. Both parents who accompanied the girl consented to an ophthalmic examination. They had no history of ophthalmic examination. The ophthalmoscopic appearance of the father was unremarkable. The mother had a visual acuity of 20/20 without correction in both eyes. Both fundi showed the same grouped pigmentation as was seen in the proband. Because of the young age of the girl, further ophthalmic investigations were performed on the mother. Fluorescein angiography disclosed blockage of background fluorescence without leakage in the late phase (Fig. 2). Results of Goldmann visual-field testing disclosed no abnormalities. As shown by electro-oculography, the ratio of the light peak to dark trough was normal. The electroretinogram showed normal cone and rod responses. The pattern reversal visual-evoked cortical potentials showed normal amplitudes and latencies.

The ten family members we examined did not have the grouped pigmentation (Fig. 3).

Discussion

The two cases in our study were typical examples of congenital grouped pigmentation of the retina. The clinical appearance is so characteristic that the disorder is easy to identify. Usually, the patients have no visual complaint, and detection is coincidental on routine ocular examination. Although grouped pigmentation of the retina has been associated with strabismus, Rieger's anomaly,[9] macula coloboma,[10] dys-

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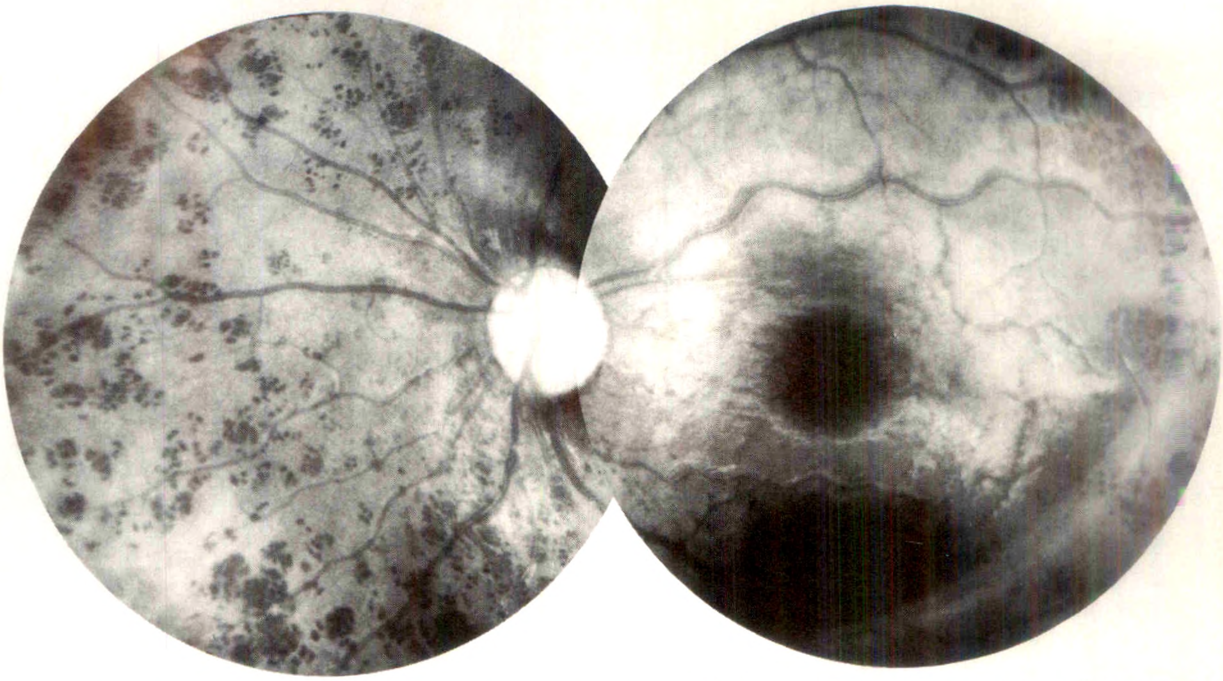

Fig. 1 (Renardel de Lavalette, Cruysberg, and Deutman). Ophthalmoscopic picture of the left eye of the proband showing typical grouped pigmentations.

chondroplasia,[11] Coats' disease, and persistent hyperplastic primary vitreous in the contralateral eye,[12] we believe these are coincidental concurrences.

Ophthalmoscopically, the lesions characteristically appear as a grouping together of spots of pigment, with two to 30 in each clump. The clumps vary in size and the larger, the more peripheral the location. The spots are regular, round to oval, and slate-gray to black. The lesions involve one or more quadrants of the fundus, except for the macula. They may be unilateral or bilateral. The lesions remain stationary and no visual-field defects or changes are observed by electroretinography.

The histopathologic features were described by Shields and Tso[13] in 1975. The lesions consist of an increased concentration of pigment granules within otherwise normal-appearing retinal pigment epithelial cells. The overlying photoreceptors are unaffected.

Forgacs and Bozin[14] described two sisters with grouped pigmentation of the macula. These patients did not have the typical lesions described in the literature and the macular localization was contrary to most previously described cases. Deutman[15] indicated that the condition in these two sisters probably represented a different condition.

Apart from two reports,[7,8] grouped pigmentation has always been described as being sporadic in nature. Casparová and Szedélyová[7] described two sisters with grouped pigmentation in all quadrants of both eyes. No other ocular or systemic abnormalities were found. De Jong and Delleman[8] described a father and son. The son had grouped pigmentation in all quadrants of both eyes and the father had pigmentations in an area inferior to the optic disk in his right fundus. The electro-oculogram showed a light peak to dark trough ratio in the lower normal range in the son. The light peak to dark trough ratio in the mother we examined was normal. De Jong and Delleman[8] proposed to place grouped pigmentation among the pattern dystrophies. We believe the term dystrophy should be reserved for disorders showing some progressive loss of visual function. In our two cases there were no accompanying ocular or other anomalies.

Because of the relatively uncommon frequency of this disorder in the general population, it seems likely that it can be have autosomal dominant inheritance with variable expression.

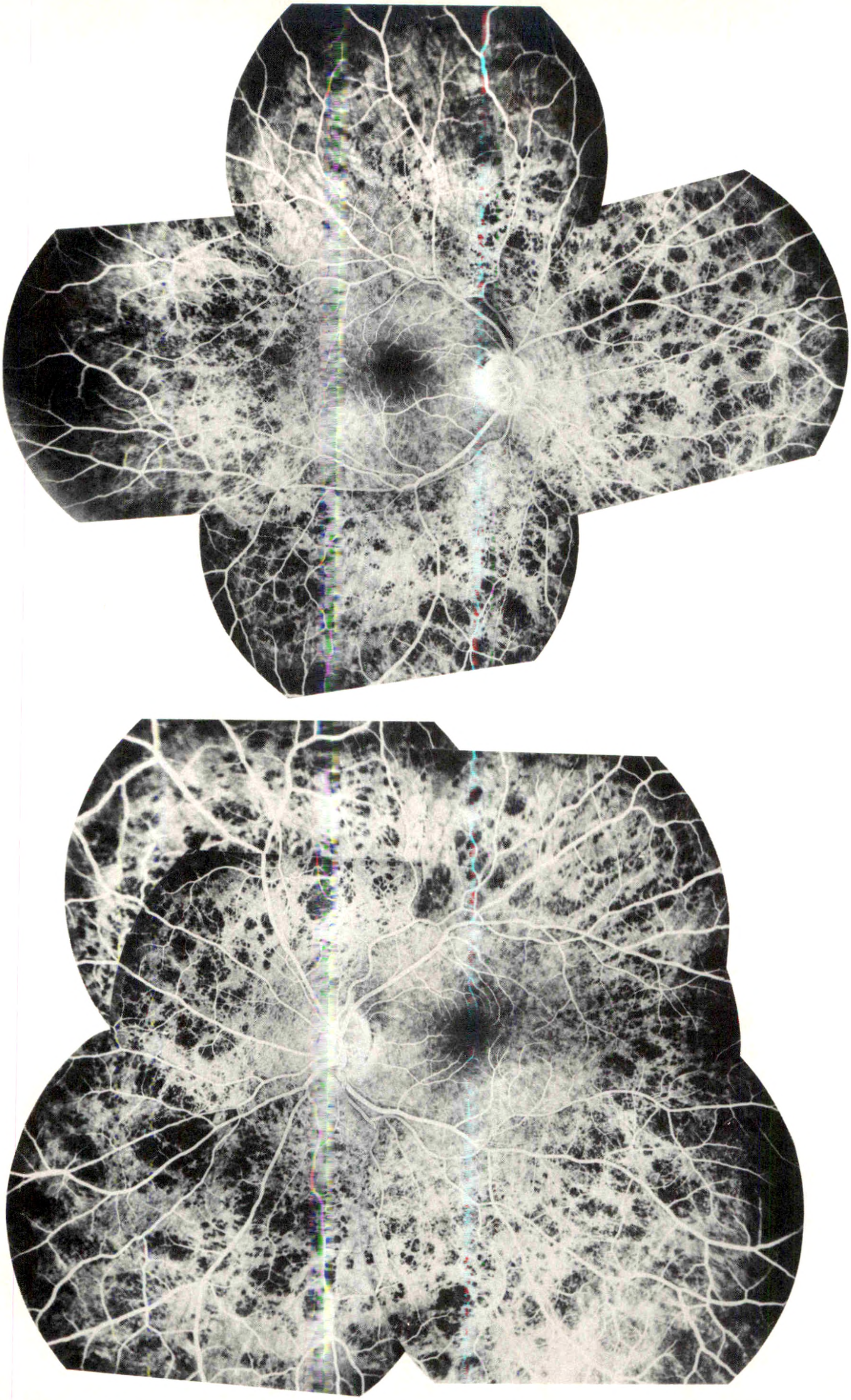

Fig. 2 (Renardel de Lavalette, Cruysberg, and Deutman). Fluorescein angiogram of the right and left eyes from the mother of the proband. Blockage of background fluorescence is shown.

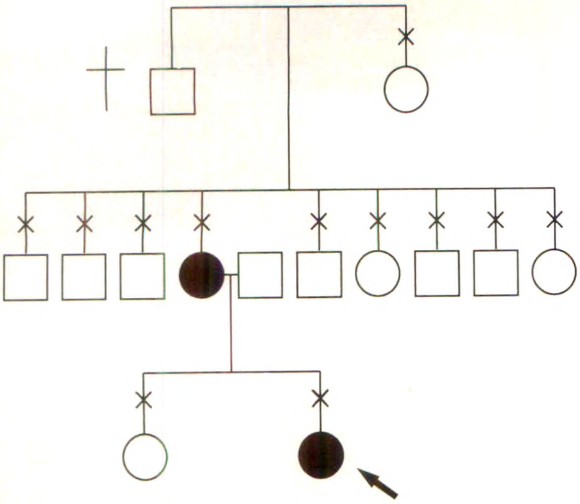

Fig. 3 (Renardel de Lavalette, Cruysberg, and Deutman). Pedigree of family with grouped pigmentation of the retina.

References

1. Mauthner, L.: Lehrbuch der Ophthalmoscopie. Wien, Austria, Tendler, 1868, p. 286.

2. Hoeg, N.: Die gruppierte Pigmentierung des Augengrundes. Klin. Monatsbl. Augenheilkd. 49:49, 1911.

3. Kraupa, E.: Studien über die Melanosis des Augapfels. Arch. Augenheilkd. 82:67, 1917.

4. Dodd, H.: Congenital pigmentation of the retina. Trans. Ophthalmol. Soc. U.K. 15:194, 1895.

5. Hedde, C.: Gruppenformige naevoide Pigmentierung der Netzhaut. Klin. Monatsbl. Augenheilkd. 647:301, 1920.

6. Mann, W. A., Jr.: Grouped pigmentation of the retina. Arch. Ophthalmol. 8:66, 1932.

7. Casparová, D., and Szedélyová, L.: Familiar occurrence of grouped pigmentations in ocular fundus. Cesk. Oftalmol. 37:406, 1981.

8. De Jong, P. T. V. M., and Delleman, J. W.: Familial grouped pigmentation of the retinal pigment epithelium. Br. J. Ophthalmol. 72:439, 1988.

9. De Jong, P. T. V. M., Delleman, J. W., Witmer, J. P., and Zeilstra, C.: Rieger's anomaly with retinal pigmentations. Ophthalmologica 178:107, 1979.

10. McGregor, I. S.: Macular coloboma with bilateral grouped pigmentation of the retina. Br. J. Ophthalmol. 39:132, 1945.

11. Collier, M.: Les manifestations oculaires associées a la dyschondroplasie d'Ollier. Bull. Soc. Ophtalmol. Fr. 4:161, 1961.

12. Fuji, M., Hayasaka, S., and Setogawa, T.: Persistent hyperplastic primary vitreous in the right eye and congenital grouped pigmentation of the retina in the left. Ophthalmologica 198:135, 1989.

13. Shields, J. A., and Tso, M. O. M.: Congenital grouped pigmentation of the retina. Histopathologic description and report of a case. Arch. Ophthalmol. 93:1153, 1975.

14. Forgacs, J., and Bozin, I.: Manifestation familiale de pigmentations groupées de la région maculaire. Ophthalmologica 152:364, 1966.

15. Deutman, A. F.: The Hereditary Dystrophies of the Posterior Pole of the Eye. Assen, the Netherlands, Van Gorcum, 1972, pp. 361–366.

Epstein-Barr Virus Antibodies in Multifocal Choroiditis and Panuveitis

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Although it has been reported that patients with multifocal choroiditis and panuveitis have serologic evidence of a chronic or persistent Epstein-Barr virus infection, our patients did not seem to have other stigmata of Epstein-Barr virus infection. To reappraise the serologic evidence of chronic Epstein-Barr virus infection, the Epstein-Barr antibody levels in 11 patients with multifocal choroiditis and panuveitis and 11 sex- and age-matched control patients were measured. Neither the antiviral capsid antigen IgG ($P = .15$) nor the antinuclear antigen ($P = .2$) antibody titers of the patients with multifocal choroiditis and panuveitis were significantly different than those of the control patients. Neither the patients with multifocal choroiditis and panuveitis nor the control patients had increased antiviral capsid antigen IgM titers. One patient with multifocal choroiditis and panuveitis and three control patients had positive anti-early antigen antibody titers ($P = .59$). The results of this study do not support the hypothesis that patients with multifocal choroiditis and panuveitis have serologic evidence of chronic or persistent Epstein-Barr virus infection as a characteristic finding.

MULTIFOCAL CHOROIDITIS and panuveitis cause discrete punched-out chorioretinal atrophic lesions and recurrent intraocular inflammation.[1] It most commonly develops in young myopic women, who are not HLA-DR2 specific.[2] Tiedeman[3] tested the Epstein-Barr virus antibody titers in ten patients with multifocal choroiditis and panuveitis and concluded that all ten had serologic evidence suggestive of chronic or persistent Epstein-Barr virus infection. However, no causal link between Epstein-Barr virus and multifocal choroiditis and panuveitis was demonstrated.

Chronic Epstein-Barr infection has been associated with various ocular and systemic disorders, including Sjögren's syndrome,[4] lymphoproliferative disorders,[5,6] nasopharyngeal carcinoma,[7] and the chronic fatigue syndrome.[8] The patients with multifocal choroiditis and panuveitis described in the literature do not seem to have had Sjögren's syndrome or a systemic illness.[1-3] To reevaluate the serologic evidence suggestive of a chronic or persistent Epstein-Barr virus infection, we tested the Epstein-Barr virus antibody titers in 11 patients with multifocal choroiditis and panuveitis and those in 11 age- and sex-matched control patients.

Patients and Methods

Multifocal choroiditis and panuveitis were diagnosed if the patient had typical, discrete, punched-out chorioretinal atrophic lesions and recurrent, clinically evident intraocular inflammation.[1] Factors that supported the diagnosis were myopia, female gender, and the lack of the HLA-DR2 specificity, but these findings were not requisite in making the diagnosis. Blood samples were drawn from 11 consecutive patients with multifocal choroiditis and 11 matched control patients who did not have evidence of multifocal choroiditis and panuveitis. Cases and control patients were recruited from the Manhattan Eye, Ear, and Throat Hospital and from the private practice of one of us (L.A.Y.). The control patients had no ocular or systemic inflammatory diseases and were individually matched to the cases by sex and

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age (± 2 years). All patients signed an informed consent for participation in the study. The consent and study design were approved by the Institutional Review Board of Manhattan Eye, Ear, and Throat Hospital.

Immunofluorescent techniques were used to quantitate viral capsid IgG, viral capsid IgM, and anti-early antigen (both restricted and diffuse components) antibody levels, and Epstein-Barr nuclear antigen antibody titers were evaluated using the ELISA method (Marlene Desquitado, M.D., written communication, Roche Biomedical Laboratories, Raritan, New Jersey, Jan. 30, 1991). All Epstein-Barr antibody titers were determined by Roche Biomedical Laboratories, Raritan, New Jersey. Positive viral antibody titers were defined by Roche Biomedical Laboratories as being greater than 1:16 for antiviral capsid antigen IgM, greater than 1:20 for the antiviral capsid antigen IgG and the diffuse and restricted components of the anti-early antigen, and greater than 56 ELISA units for nuclear antigen. Treatment of one of the patients with multifocal choroiditis and panuveitis had just been initiated at the time of blood collection. Low-dose corticosteroids were administered orally. None of the rest of the patients with multifocal choroiditis and panuveitis and none of the control patients were being treated with any immunosuppressive drugs at the time of the serologic tests.

Categorical data were analyzed using the Fisher's exact test.[9] Where appropriate, geometric mean antibody titers were calculated.[10] The logarithm to base 2 was taken of the antibody titers and compared, using the paired *t*-test.[10] The nuclear antigen antibody titers were compared by use of a paired *t*-test, which used the untransformed ELISA units. A P value of less than .05 was considered significant.

Results

At the time of examination, the patients had chorioretinal lesions in varying states of activity, but all 11 patients had inflammatory cells in the vitreous humor. Of the 11 patients, nine were women and two were men. None of the 11 patients had the HLA-DR2 specificity; eight of these had been subjects in a previous report.[2] Seven of the patients had a myopic refractive error of greater than −1 diopters spherical equivalent. The mean age was 36.5 years (standard deviation, 11.6 years). The geometric mean antiviral capsid antigen IgG antibody titer was 150.2 for cases and 80 for control patients, but the difference was not significant (P = .15) (Table). No case or control patient had a positive antiviral capsid antigen IgM titer. Although the best point estimate from this study for the true prevalence of positive antiviral capsid antigen IgM titers in patients with multifocal choroiditis and panuveitis was 0%, the 95% binomial confidence interval extended from 0% to 28.4%.

One patient with multifocal choroiditis and panuveitis had a positive antibody titer for both the antirestricted component (1:20) and the antidiffuse component (1:20) of the early antigen. One control patient had a positive antibody titer to the antirestricted component (1:20) and the antidiffuse component (1:80) of the anti-early antigen. Two additional control patients had positive antidiffuse components to the early antigen; one had a titer of 1:20 and the other had a titer of 1:80. In total, one case and three control patients had positive anti-early antigen titers. Although the abnormal titers were more common in the control patients, the proportion was not significantly different (P =

TABLE

EPSTEIN-BARR ANTIBODY TITERS IN MULTIFOCAL CHOROIDITIS AND PANUVEITIS

ANTIBODIES	PATIENTS WITH MULTIFOCAL CHOROIDITIS AND PANUVEITIS (N=11)	CONTROL PATIENTS (N=11)	P VALUE
Antiviral capsid antigen IgG (geometric mean titers)	150.2	80	.15
Antiviral capsid antigen IgM (No. positive)	0	0	—
Anti-early antigen (No. positive)	1	3	.59
Antinuclear antigen (Mean ELISA titers)	161.7	266.6	.20

.59). The best point estimate from this study for the true prevalence of positive anti-early antigen titers in patients with multifocal choroiditis and panuveitis was 9.1%, and the 95% binomial confidence interval extended from 0.23% to 41.3%. The mean ELISA nuclear antigen titer for cases was 161.7 and the mean titer for control patients was 266.6, which was not significantly different (P = .2). The one patient with multifocal choroiditis and panuveitis who was treated with corticosteroids at the time of the serologic tests did not have positive early antigen titers.

Discussion

In primary Epstein-Barr virus exposure, B-lymphocytes are infected and become transformed by the virus into immortalized cell lines. The infected B-lymphocytes are capable of continuous proliferation, expression of Epstein-Barr nuclear antigen, and secretion of antiviral capsid antigen IgG.[11,12] In early stages of infection, antiviral capsid antigen IgM and anti-early antigen antibodies are also produced. The infected B-lymphocytes are potent activators of autologous T-lymphocytes, inducing preferential clonal expansion of suppressor/cytotoxic T-cells.[11] In vitro, these T-cells appear to inhibit proliferation of the infected B-lymphocytes through both cytotoxic T-lymphocyte activity and the release of γ-interferon.[13,14] With resolution of the primary infection, antiviral capsid antigen IgM and anti-early antigen production ceases. A small pool of infected, immortalized B-lymphocytes remains associated with the production of antiviral capsid antigen IgG and anti-nuclear antigen antibodies.[15]

Epithelial cells in the basal and intermediate layers of the oropharyngeal and nasopharyngeal epithelium have receptors for the Epstein-Barr virus.[11] In asymptomatic individuals, Epstein-Barr virus continues to multiply in the pharyngeal epithelium. There is indirect evidence that suggests that the cell-mediated immune system has some ability to control viral replication in pharyngeal epithelial cells.[16,17] At any one time, 10% to 60% of healthy individuals who are Epstein-Barr virus seropositive have infectious virus recoverable from their oropharyngeal washings,[11] and over a period of time, more than 90% of healthy seropositive individuals secrete infectious virus from their oropharynx.[18] Release of the Epstein-Barr virus may in turn newly infect additional B-lymphocytes in the individual. The pool of immortalized and newly infected B-lymphocytes, however, appears to be tightly controlled by the suppressor/cytotoxic T-lymphocytes.[11]

Altering the T-cell function in a patient may alter the control, allowing the level of B-lymphocyte infection to increase. With an increase in infection, the antiviral capsid antigen IgG increases, the level of Epstein-Barr nuclear antigen decreases, and antiviral capsid antigen IgM and anti-early antigen antibodies appear.[12,19] Lengthy immunosuppressive therapy or certain disease states affecting cell-mediated immunity have been associated with profound and long-lasting alterations of Epstein-Barr virus antibody production.[5,12,19,20] Demonstration of abnormal Epstein-Barr virus antibody titers in a disease state, therefore, does not necessarily imply a causal link between Epstein-Barr virus and the disease. The abnormal antibody titers may well be a nonspecific response to immune alterations.

The diagnosis of chronic Epstein-Barr virus infection is best supported when both the antiviral capsid antigen IgM and anti-early antigen antibody levels are abnormal.[11,12] Tiedeman[3] tested ten patients and eight control patients, and found positive IgM or anti-early antigen antibody titers in the patients with multifocal choroiditis and panuveitis, but not in the control patients. These results are at variance with the series described in this report. One of several possible factors may help explain this disagreement. The antibody titers considered positive were not defined in Tiedeman's study. Only three of the ten patients in Tiedeman's study actually had antiviral capsid antigen IgM titers greater than 1:10. Additionally, it was not stated if the patients with multifocal choroiditis and panuveitis were being treated with immunosuppressive medications in that study.

Multifocal choroiditis and panuveitis constitute a recently described, but incompletely defined disorder. One group of investigators may define the disease differently than another group. Indeed, multifocal choroiditis and panuveitis may have more than one cause producing a morphologically indistinguishable statement in the fundus. Because multifocal choroiditis and panuveitis are relatively uncommon and both Tiedeman's and our study suffer from small sample size, selection bias might have preferentially skewed the results in either or both of these studies.

None of the patients with multifocal choroiditis and panuveitis in this study were treated with long-term immunosuppressive medications at the time of their Epstein-Barr virus antibody determinations. We found no statistical difference in the antiviral capsid antigen IgG, antiviral capsid antigen IgM, anti-early antigen antibody titers, or antinuclear antigen antibody titers of the patients with multifocal choroiditis and panuveitis in this study compared to the same variables in their age- and sex-matched control patients. Because of the small sample size, not detecting a statistically significant difference between the two groups does not completely rule out the possibility that there might be a difference or that there might be a subgroup of patients with multifocal choroiditis and panuveitis who do have abnormal Epstein-Barr antibody titers. Further analysis of a larger group of patients would be required to evaluate this possibility, but recruiting enough patients from a single institution might be difficult. In the serologic testing of the patients in this study, however, no patient or control patient had abnormal levels of both antiviral capsid antigen IgM and anti-early antigen antibody. Three control subjects and only one patient with multifocal choroiditis and panuveitis had abnormal anti-early antigen antibody levels. Therefore, the results of this study do not support the hypothesis that patients with multifocal choroiditis and panuveitis have a chronic or persistent Epstein-Barr virus infection as a characteristic finding.

References

1. Dreyer, R. F., and Gass, D. M.: Multifocal choroiditis and panuveitis. A syndrome that mimics ocular histoplasmosis. Arch. Ophthalmol. 102:1776, 1984.

2. Spaide, R. F., Skerry, J. E., Yannuzzi, L. A., and DeRosa, J. T.: Lack of the HLA-DR2 specificity in multifocal choroiditis and panuveitis. Br. J. Ophthalmol. 74:536, 1990.

3. Tiedeman, J. S.: Epstein-Barr viral antibodies in multifocal choroiditis and panuveitis. Am. J. Ophthalmol. 103:659, 1987.

4. Fox, R. I., Pearson, G., and Vaughan, J. H.: Detection of Epstein-Barr virus associated antigens and DNA in salivary gland biopsies from patients with Sjögren's syndrome. J. Immunol. 137:3162, 1986.

5. Geller, R. H., and Grose, C.: Epstein-Barr virus. The hematologic and oncologic consequences of virus-host interaction. CRC. Crit. Rev. Oncol. Hematol. 9:149, 1989.

6. Crawford, D. H., Thomas, J. A., Janossy, G., Sweny, P., Fernando, O. N., Morehead, J. F., and Thompson, J. H.: Epstein-Barr virus nuclear antigen positive lymphoma after cyclosporin A treatment in patient with renal allograft. Lancet 1:1355, 1980.

7. Klein, G., Geering, G., Old, L. J., Henle, G., Henle, W., and Clifford, P.: Comparison of the anti-EBV titer and the EBV-associated membrane reactive and precipitating antibody levels in the sera of Burkitt lymphoma and nasopharyngeal carcinoma patients and controls. Int. J. Cancer 5:185, 1970.

8. Buchwald, D., Sullivan, J. L., and Komaroff, A. L.: Frequency of "chronic active Epstein-Barr virus infection" in a general medical practice. JAMA 257:2303, 1987.

9. Fleiss, J. L.: Statistical Methods for Rates and Proportions, ed. 2. New York, John Wiley & Sons, Inc., 1981, pp. 112–137.

10. Paul, J. R., and White, C.: Serological Epidemiology. New York, Academic Press, Inc., 1973, pp. 19–32.

11. Tosato, G.: The Epstein-Barr virus and the immune system. Adv. Cancer Res. 49:75, 1987.

12. Thorley-Lawson, D. A.: Immunological responses to Epstein-Barr virus infection and the pathogenesis of EBV-induced diseases. Biochim. Biophys. Acta 948:263, 1988.

13. Hasler, F., Bluestein, H. G., Zvaifler, N. J., and Epstein, L. B.: Analysis of the defects responsible for the impaired regulation of Epstein-Barr virus-induced B cell proliferation by rheumatoid arthritis lymphocytes. I. Diminished gamma interferon production in response to autologous stimulation. J. Exp. Med. 157:173, 1983.

14. Slovin, S. F., Schooley, R. T., and Thorley-Lawson, D. A.: Analysis of cellular immune response to EBV by using cloned T cell lines. J. Immunol. 130:2127, 1983.

15. Sugden, B., Phelps, M., and Domoradzki, J.: Epstein-Barr virus DNA is amplified in transformed lymphocytes. J. Virol. 31:590, 1979.

16. Strauch, B., Andrews, L., Siegel, N., and Miller, G.: Oropharyngeal excretion of Epstein-Barr virus by renal transplant recipients and other patients treated with immunosuppressive drugs. Lancet 1:234, 1974.

17. Gaston, J. S., Rickinson, A. B., and Epstein, M. A.: Epstein-Barr virus specific T-cell memory in renal-allograft recipients under long-term immunosuppression. Lancet 1:923, 1982.

18. Yao, Q. Y., Rickinson, A. B., and Epstein, M. A.: A re-examination of the Epstein-Barr virus carrier state in healthy seropositive individuals. Int. J. Cancer 35:35, 1985.

19. Henle, W., and Henle, G.: Epstein-Barr virus-specific serology in immunologically compromised individuals. Cancer Res. 41:4222, 1981.

20. Lange, B., Henle, W., Meyers, J. D., Yang, L. C., August, C., Koch, P., Arbeter, A., and Henle, G.: Epstein-Barr virus-related serology in marrow transplant recipients. Int. J. Cancer 26:151, 1980.

Subepithelial Infiltrates in *Acanthamoeba* Keratitis

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Six patients had *Acanthamoeba* keratitis that manifested an unusual type of subepithelial corneal infiltrate late in the course of the disease. These infiltrates occurred in the anterior corneal stroma, often in a location removed from the site of infection. In four of these patients the infiltrates occurred with no other clinical signs of inflammation. Two patients had mild foreign-body sensation that resolved despite the persistence of the subepithelial infiltrates. The infiltrates resolved with topical corticosteroid therapy in three patients; however, in two of these three patients the infiltrates recurred when corticosteroid therapy was tapered or discontinued. The subepithelial infiltrates appeared and behaved similarly to those associated with viral and chlamydial corneal infections. An immunologic mechanism may be responsible for these unusual delayed-in-onset infiltrates.

ACANTHAMOEBA KERATITIS is a serious, often misdiagnosed, corneal infection that can follow a protracted devastating course. Clinically, it may appear as irregularity of the epithelium, cysts and lines, recurrent epithelial erosions, stromal infiltrates that sometimes have a ring-shaped appearance, and radial keratoneuritis.[1-9]

We encountered six cases of *Acanthamoeba* keratitis with infiltrates that were unusual because they were subepithelial and occurred late in the course of the disease. Three representative cases are described herein. An immunologic mechanism may be responsible for these infiltrates in *Acanthamoeba* keratitis.

Case Reports

Case 1

A 14-year-old girl who was a daily-wear, soft contact-lens wearer developed decreased vision, redness, and irritation in her left eye in October 1988. During the next three months, her symptoms gradually worsened. She was treated unsuccessfully with a variety of eyedrops, including antibiotics, trifluridine, and prednisolone 1%. On Jan. 10, 1989, she had a visual acuity with a pinhole correction of 20/60 in her left eye. Slit-lamp examination disclosed a central epithelial defect with an underlying anterior stromal infiltrate approximately 3 mm in diameter (Fig. 1). There were numerous epithelial lesions immediately surrounding the central stromal infiltrate and diffuse epithelial edema. The anterior chamber was without cell

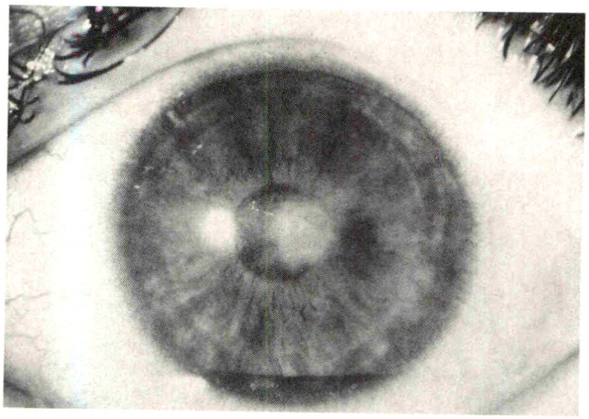

Fig. 1 (Holland and associates). Case 1. Central anterior stromal infiltrate at the time of initial manifestation.

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and flare. The patient underwent a diagnostic central superficial keratectomy. Specimens were sent for smear and cultures for bacteria, fungus, and *Acanthamoeba* sp. The patient was treated for presumed *Acanthamoeba* keratitis with miconazole 1%, neomycin, and propamidine isethionate eyedrops that were instilled every hour. Ketoconazole was also prescribed, 200 mg orally every day. Routine smears and cultures were negative. The calcofluor white-stained smear showed several *Acanthamoeba* cysts.

By the fourth day of treatment, the epithelial defect had diminished in size, the infiltrate had consolidated, and the patient was more comfortable. She continued instilling the drop medications every two hours and the ketoconazole at the same dosage and frequency. During the ensuing three weeks, the epithelial defect healed, the central infiltrate gradually resolved, but a peripheral anterior midstromal corneal haze from the 3:00 to 8:00 o'clock meridian was detected. Anterior stromal neovascularization was also seen in the area of stromal haze. The overlying epithelium was intact. The peripheral stromal haze and neovascularization gradually became more pronounced. Dexamethasone, topically four times a day, was added to her regimen. The peripheral infiltrate resolved quickly during the next three days and the corticosteroid drop regimen was slowly tapered. By June 1989, the patient's visual acuity had improved to 20/25 and there was a superficial central stromal scar. The peripheral corneal clouding and neovascularization had regressed completely. She continued propamidine isethionate and neomycin drops once a day, and the corticosteroid drops were discontinued. In August 1989, she was asymptomatic with a visual acuity of 20/25, but numerous subepithelial and anterior stromal infiltrates extended 360 degrees in the peripheral cornea (Fig. 2). The overlying epithelium remained intact. Dexamethasone drops were instilled every four hours, and propamidine isethionate and neomycin were continued. The subepithelial infiltrates resolved completely during the following week. The topical antiamebic agents were discontinued. Over the next few months the corticosteroid drops were tapered to prednisolone 1/8% every other day. In April 1990, the peripheral subepithelial infiltrates recurred. The epithelium was still intact and the patient was asymptomatic at that time. She was instilling prednisolone 1/8% drops every other day. The prednisolone drop schedule was increased to twice a day. Again, the subepithelial infiltrates resolved during the course of one week. At her last examination in November 1990, the patient's visual acuity was 20/25 in her left eye. She continues to instill prednisolone drops three times a week and has remained free of active *Acanthamoeba* infection and inflammation.

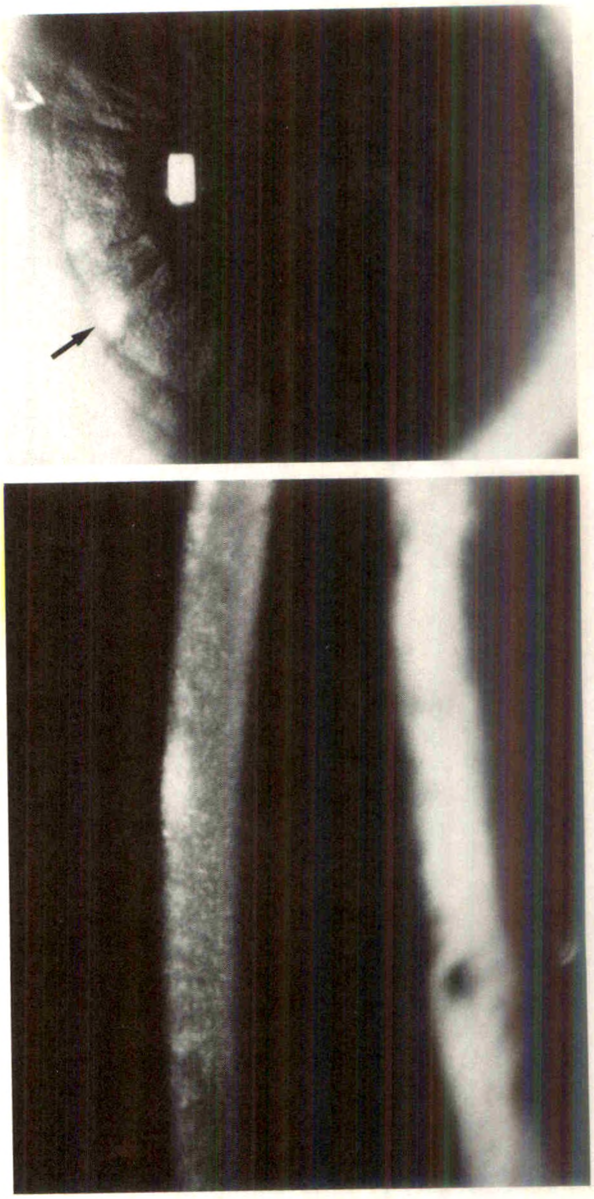

Fig. 2 (Holland and associates). Case 1. Top, Subepithelial infiltrates in the peripheral cornea occurred 15 months after diagnosis and initial treatment of *Acanthamoeba* (arrow). Central cornea had inactive anterior stromal scar. Bottom, Slight beam showing subepithelial location of the infiltrate.

Case 2

A 20-year-old woman, who was a daily-wear, soft contact-lens wearer, developed redness and pain in her right eye. During the following month she was treated empirically with antiviral, antibiotic, and corticosteroid drops without clinical improvement.

At the time of her examination on Oct. 13, 1988, she had been applying vidarabine ointment five times a day and homatropine twice a day. Her visual acuity was 20/200 in the right eye with pinhole improvement to 20/40. Visual acuity in the left eye was 20/30 with pinhole improvement to 20/20. External examination disclosed marked ciliary flush in the right eye. Corneal sensation was diminished. Slit-lamp examination disclosed a dendritic epithelial lesion in the nasal midperipheral cornea, which accumulated fluorescein dye but was not associated with an epithelial defect. Corneal nerves emanating from the inferotemporal and superotemporal corneoscleral limbus appeared inflamed into the paracentral cornea. The anterior chamber was without cell and flare.

Corneal scrapings, contact lenses, and the contact-lens case were sent for cultures for *Acanthamoeba*. A regimen was begun of hourly topical propamidine isethionate and neomycin therapy. Sulindac, 200 mg orally twice a day, was started for control of ocular pain. Cultures of the corneal scrapings and contact-lens case yielded *Acanthamoeba* sp. By Oct. 15, 1989, the patient's discomfort improved markedly. On slit-lamp examination, the density of the anterior stromal infiltrates had diminished considerably. By Oct. 24, 1989, the radial keratoneuritis had resolved. The propamidine isethionate and neomycin therapy was continued until Nov. 14, 1989. Visual acuity was 20/20, and slit-lamp examination disclosed only a faint haze in the anterior stroma in the superotemporal midperiphery of the right cornea. Examination on April 26, 1990, showed 15 to 20 subepithelial infiltrates involving the superior and central cornea (Fig. 3). The patient was asymptomatic with no discomfort or blurred vision. Visual acuity of the right eye was 20/20. The possibility of recurrence of *Acanthamoeba* infection was considered, and a regimen of propamidine isethionate and neomycin drops, administered hourly, was started. By May 15, 1990, the lesions had lessened in density, and the propamidine isethionate and neomycin drop regimen was slowly tapered. On June 12, 1990, the patient's visual acuity was 20/20. Slit-lamp examination showed persistence of the subepithelial infiltrates.

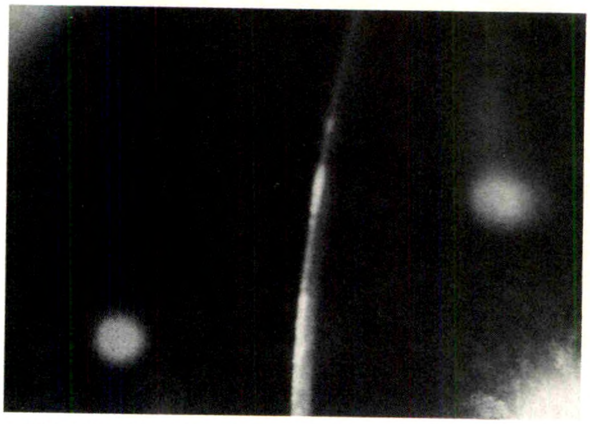

Fig. 3 (Holland and associates). Case 2. Subepithelial infiltrates in the midperipheral cornea eight months after diagnosis and initial treatment of *Acanthamoeba* keratitis.

Case 3

A 40-year-old woman, who was a gas-permeable contact-lens wearer, noticed the onset of redness, tearing, photophobia, and a white line that appeared across her right cornea beginning on June 17, 1988. While on vacation the previous week, she had rinsed her contact lenses in well water. Her ophthalmologist treated her for eight days with medications including tobramycin, gentamicin, sulfacetamide 10%, and prednisolone 0.25% eyedrops, and fortified tobramycin and cefazolin eyedrops without improvement of the condition. Routine cultures of scrapings of the cornea taken on the eighth day did not yield any organisms. Six days after her topical medications were discontinued, examination on July 17, 1988, disclosed visual acuity of R.E.: 20/60 and L.E.: 20/20. She had marked upper and lower eyelid edema, diffuse bulbar conjunctival hyperemia, and a central anterior stromal corneal infiltrate in the right eye. Epithelium overlying the infiltrate was intact. There was a mild cellular reaction in the anterior chamber. A diagnosis of herpetic keratitis was considered, and a regimen was begun of trifluridine and prednisolone 1% eyedrops, which she instilled in the right eye four times a day. The corneal infiltrates remained unchanged over the course of one week of therapy. The cornea was scraped and cultured for *Acanthamoeba* sp. *Acanthamoeba* organisms were identified on modified Wright's stain. The patient began instilling miconazole 1% eyedrops four times a day and propamidine isethionate and bacitracin eyedrops every half hour in the right eye. The culture yielded *Acanthamoeba* sp. Five days after institution of antiamebic therapy, mild stromal edema was visible. Visual acuity in the right eye deteriorated to 3/200. Over the next several days the patient's symptoms of pain, photophobia, and tearing markedly improved. Visual acuity gradually improved to 20/70. On slit-lamp examination the stromal edema had improved except for a small area temporally. The corneal infiltrate had cleared markedly, and the inflammation resolved in the anterior chamber. The bacitracin and propamidine isethionate eyedrops were tapered to four times a day, and the miconazole eyedrops were discontinued. Epithelial cystic areas temporally persisted and were scraped. Tissue sent for culture yielded *Acanthamoeba* organisms. The propamidine isethionate and neomycin eyedrops were increased to every hour. By Aug. 31, 1988, visual acuity had improved to 20/25 in the affected, right eye. The focal epithelial changes had diminished, and the anterior chamber was without cell and flare. The neomycin and propamidine isethionate eyedrops were tapered to four times a day, and by Sept. 21, 1988, they were discontinued. Approximately one week later the patient developed a mild foreign-body sensation. Visual acuity had decreased slightly to 20/40. Examination of the cornea showed numerous diffuse subepithelial infiltrates. No treatment was begun at that time. One week later the infiltrates were subepithelial with mild conjunctival irritation. The patient was followed up until March 18, 1989, without further treatment. The subepithelial infiltrate had become fainter and the conjunctival inflammation had subsided.

Discussion

In five of our six patients the subepithelial infiltrates were diffuse. The subepithelial infiltrates in the other patient were localized to the midperipheral and peripheral region of one quadrant. Moore and coworkers[10] observed anteriorstroma infiltrates in four patients during acute *Acanthamoeba* keratitis, which responded to topical antiamebic therapy. In contrast, the cases in our series were characterized by the relatively late appearance of the subepithelial infiltrates and the favorable response that several patients showed to topical corticosteroids after antiamebic therapy had been discontinued.

Subepithelial infiltrates could occur in association with *Acanthamoeba* keratitis for many reasons. They could be attributed to an inflammatory response against active *Acanthamoeba* infection. *Acanthamoeba* infection often follows a waxing and waning course. This may be the result in part of the encystment/excystment cycle of the organism, because infection-associated inflammation may exacerbate upon transformation of the organism from the dormant cystic stage to the active trophozoite form.[8,10] The subepithelial infiltrates observed in our patients may possibly represent inflammation associated with emergence of trophozoites from their cystic form. This may be true even though the infiltrates occurred in a location removed from the clinically apparent infection in two of our patients. Areas of clinically uninvolved cornea have been shown to harbor cysts on histopathologic examination.[8,11] However, clinical improvement in the absence or tapering of antiamebic therapy in our patients militated against active infection. Additionally, the patient described in Case 1 was treated solely with corticosteroid eyedrops and showed a rapid response to corticosteroid therapy. Although some evidence suggests that corticosteroids may induce *Acanthamoeba* encystment,[12] an active infection would most likely result in eventual worsening of the disease, which did not occur.

The subepithelial infiltrates may also have been caused by adverse reactions to topical medication. Propamidine isethionate, the antiamebic agent administered in our three patients, can give rise to toxic corneal changes with prolonged use.[13] However, it has been reported to cause an epithelial microcystic keratopathy and not subepithelial infiltrates. Other medications and their preservatives, such as thimerosal, may cause a hypersensitivity reaction that clinically appears as subepithelial infiltrates.[14,15] In our series, the patient described in Case 1 was on a tapering regimen of antiamebic therapy when the infiltrates first occurred, and they later recurred after therapy had been discontinued. The patients described in Cases 2, 3, and 6 had stopped topical medications when the lesions were first noted. These temporal relationships discredit drug toxicity or hypersensitivity as a possible explanation for the subepithelial infiltrates.

Possibly, the infiltrates may have been the result of an immune reaction directed against *Acanthamoeba* antigens. *Acanthamoeba* organisms and their cystic remnants can evoke an inflammatory response that may be immunologic. The subepithelial infiltrates observed in our patients may have been caused by residual *Acanthamoeba* antigens remaining in the epithelium and anterior stroma after the organisms had been killed. This process would be similar to the development of subepithelial infiltrates in association with viral and chlamydial disease. Lastly, we cannot exclude the possibility that our patients had a concomitant corneal infection attributed to viral or chlamydial agents. Five of our patients gave no history of having been exposed to anyone with a history of keratoconjunctivitis or ocular infection. Although the patient described in Case 3 volunteered that her son had had a red eye during the course of her *Acanthamoeba* corneal infection, her subepithelial infiltrates were seen too early to be attributed to transmission of another infection contracted from her son. Further, she had no history of discharge in an otherwise uninflamed eye, which also causes doubt about a possible secondary viral or chlamydial infection.

Ophthalmologists should be aware of the occurrence of subepithelial infiltrates in patients with *Acanthamoeba* keratitis. It is important to know that these may not be caused by active infection requiring antiamebic treatment but may be attributed to an immunologic process.

References

1. Moore, M. B., and McCulley, J. P.: *Acanthamoeba* keratitis associated with contact lenses. Six consecutive cases of successful management. Br. J. Ophthalmol. 73:271, 1989.
2. Hirst, W. O., Green, W. R., Merz, W., Kaufman, C., Visvesvara, G. S., Jensen, A., and Howard, M.: Management of *Acanthamoeba* keratitis. A case report and review of the literature. Ophthalmology 91:1105, 1984.
3. Jones, D. B., Visvesvara, G. S., and Robinson, N. M.: *Acanthamoeba polyphaga* keratitis and *Acanthamoeba* uveitis associated with fatal meningoencephalitis. Trans. Ophthalmol. Soc. U.K. 95:221, 1975.
4. Cohen, E. J., Buchanan, H. W., Laughrea, P. A., Adams, C. P., Galentine, P. G., Visvesvara, G. S., Folberg, R., Arentsen, J. J., and Laibson, P. R.: Diagnosis and management of *Acanthamoeba* keratitis. Am. J. Ophthalmol. 100:389, 1985.
5. Watson, P. G.: Amebic infection of the eye. Trans. Ophthalmol. Soc. U.K. 95:204, 1975.
6. Case records of Massachusetts General Hospital. Case 10-1985. N. Engl. J. Med. 312:634, 1985.
7. Hamburg, A., and De Janckheere, J. F.: Amebic keratitis. Ophthalmologica 181:74, 1980.
8. Auran, J. D., Stan, M. B., and Jakobiec, F. A.: *Acanthamoeba* keratitis. A review of the literature. Cornea 6:2, 1987.
9. Theodore, F. H., Jakobiec, F. A., Juechter, K. B., Ma, P., Troutman, R. C., Pang, P. M., and Iwamoto, T.: The diagnostic value of a ring infiltrate in acanthamoebic keratitis. Ophthalmology 92:1471, 1985.
10. Moore, M. B.: *Acanthamoeba* keratitis and contact lens wear. The patient is at fault. Cornea [Suppl.] 9:533, 1990.
11. Key, S. N., III, Green, W. R., Willaert, E., Stevens, A. R., and Key, S. N., Jr.: Keratitis due to *Acanthamoeba castellani*. A clinicopathologic case report. Arch. Ophthalmol. 98:475, 1980.
12. Osato, M., Robinson, N., Wilhelmus, K., and Jones, K.: Morphogenesis of *Acanthamoeba castellani*. Titration of the steroid effect. Invest. Ophthalmol. Vis. Sci. 27:37, 1986.
13. Johns, K. J., Head, W. S., and O'Day, D. M.: Corneal toxicity of propamidine. Arch. Ophthalmol. 106:68, 1988.
14. Wilson, L. A., McNatt, J., and Reitschel, R.: Delayed hypersensitivity to thimerosal in soft contact lens wearers. Ophthalmology 88:804, 1981.
15. Binder, P. S., Rasmussen, D. M., and Gordon, M.: Keratoconjunctivitis and soft contact lens solutions. Arch. Ophthalmol. 99:87, 1981.

Demonstration of Herpes Simplex Virus DNA in Idiopathic Corneal Endotheliopathy

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A 56-year-old man developed idiopathic corneal endotheliopathy. The lesion consisted of severe stromal edema at the lower half of the cornea along with a number of associated keratic precipitates and steadily progressed to the upper half of the cornea. By polymerase chain reaction, herpes simplex virus DNA was demonstrated in the aqueous humor of this patient. Corneal stromal edema was resolved in response to treatment with topically applied and systemic acyclovir. Herpes simplex virus DNA was repeatedly demonstrated in the aqueous humor when the endothelial lesion recurred later. This evidence strongly indicates that this unique endothelial disorder is of viral origin.

SINCE THE REPORT by Khodadoust and Attarzadeh in 1982,[1] a presumed unique clinical entity defined as autoimmune corneal endotheliopathy has been recognized with increasing frequency.[1-8] This disease is characterized by corneal stromal edema progressing centripetally from the periphery and a slow-moving line of keratic precipitates succeeded by edema formation, and has been given various names such as acute idiopathic corneal endotheliitis,[4] idiopathic corneal endotheliopathy,[5] and idiopathic sectorial endotheliitis.[7] Khodadoust and associates[1,8] assumed that the disease resulted from autoimmune reaction in the corneal endothelium. However, other lines of evidence have suggested a viral origin. These included the demonstration of herpes virus particles in the corneal endothelium[2] or positive immunofluorescence of herpes simplex virus in cells obtained from the aqueous humor.[6] Our study demonstrated the presence of herpes simplex virus DNA in the aqueous humor of a patient with idiopathic corneal endotheliopathy.

Case Report

On Nov. 3, 1989, a 56-year-old man visited an ophthalmologist complaining of blurred vision in his left eye that had lasted for one week. He had suffered from Wegener's granulomatosis for almost ten years and had been on a long-term regimen of cyclophosphamide and prednisolone. He developed chronic renal failure seven years previously and had undergone hemodialysis.

His best-corrected visual acuity was 20/20 in the left eye. His primary-care physician observed the stromal edema in the lower third of the cornea that was associated with numerous keratic precipitates. He was then treated with corticosteroid (0.1% betamethasone) eyedrops four times a day and antibiotic (ofloxacin) eyedrops four times a day for the next two weeks, without remarkable improvement.

On Nov. 28, 1990, he was referred to the Osaka University Clinic for consultation. On this visit, his best-corrected visual acuity was L.E.: 20/25 and R.E.: 20/20. Slit-lamp examination of his left eye disclosed stromal edema that was prominent in the approximate lower half of the cornea (Fig. 1, top left) and a number of keratic precipitates at the area of corneal edema. Striate keratopathy was prominent. A line of keratic precipitates was formed at the boundary of the corneal edema. Additionally, a

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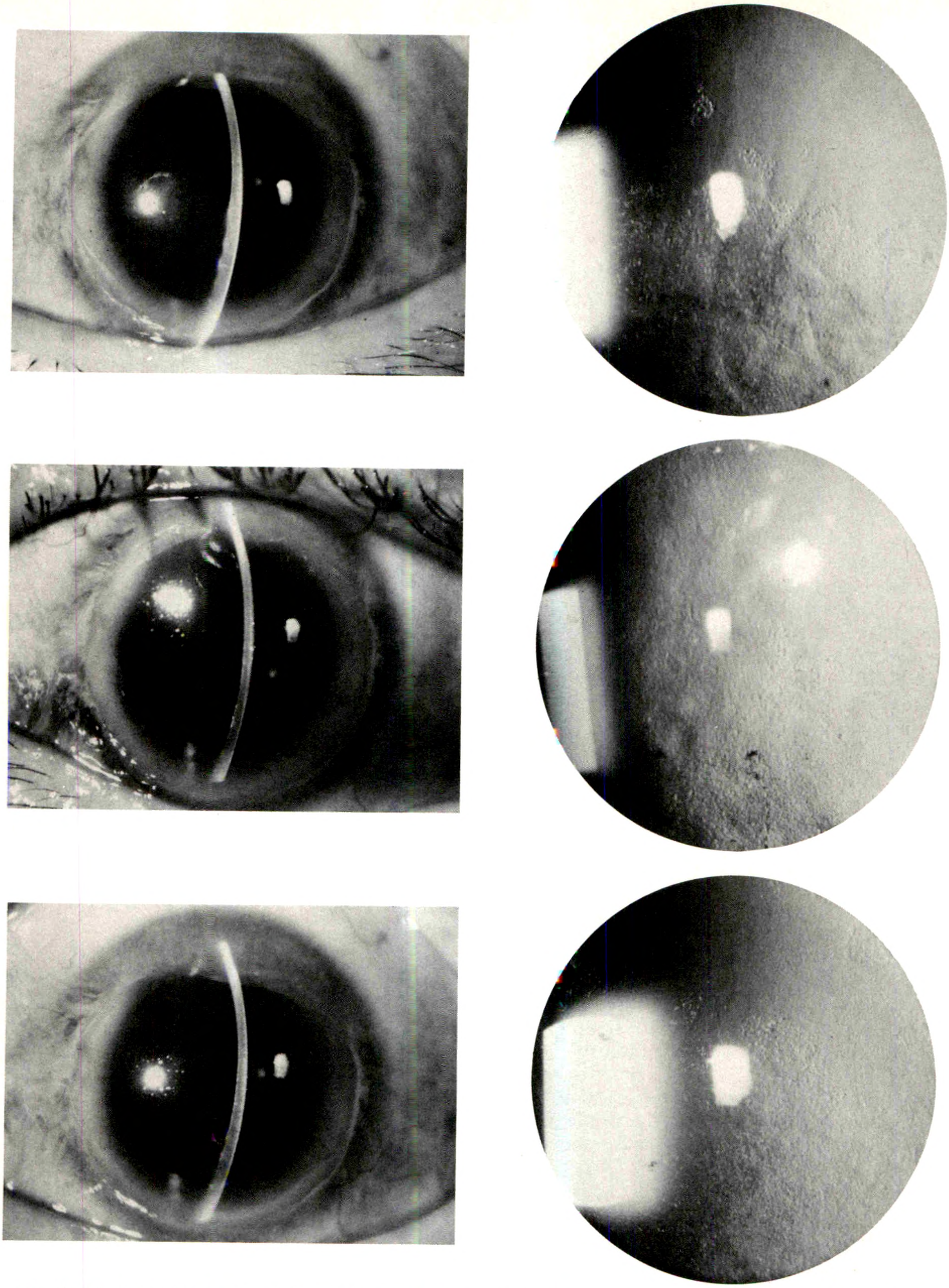

Fig. 1 (Ohashi and associates). Top left, A marked stromal edema was prominent at the inferior half of the cornea. The conjunctiva was not hyperemic. Top right, Retroillumination shows epithelial edema occupying the inferior half and numerous keratic precipitates. A few satellite lesions were noted at the superior half of the cornea. Middle left, A stromal edema was resolved. Middle right, Epithelial edema subsided and most of the keratic precipitates disappeared. Bottom left, A stromal edema was again noted at the inferior half of the cornea. Bottom right, Retroillumination shows reappearance of epithelial edema occupying the inferior half and numerous keratic precipitates.

few coin-shaped satellite lesions consisting of keratic precipitates were scattered in the upper half of the corneal endothelium (Fig. 1, top right). Corneal stroma was free of cellular infiltrates and opacities. Anterior chamber reaction was minimal and the conjunctiva was not hyperemic. Specular microscopy disclosed a marked enlargement of the corneal endothelium.

In addition to these abnormalities, circumferential thinning of the peripheral cornea with superficial new vessel formations was evident. The lesion itself was free of inflammatory cells and easily identified as an old scar resulting from previous marginal infiltrates of Wegener's granulomatosis. The lens, vitreous humor, and fundus were clinically normal. His right eye was normal except that it had the same corneal scar as that of the left eye.

These characteristic clinical manifestations led to the diagnosis of idiopathic corneal endotheliopathy. As the use of corticosteroids alone did not appear to be effective, topical application of acyclovir ointment five times a day was added to the treatment regimen in an attempt to suppress herpesvirus proliferation. After obtaining informed consent from the patient, an aliquot of the aqueous humor was aspirated for DNA amplification with polymerase chain reaction.

Corneal stromal edema and keratic precipitates subsided slightly over the next few weeks. However, the patient's compliance for topical application was unreliable. He was then hospitalized to receive intravenous administration of acyclovir (750 mg/day) as well as exact topical application of acyclovir five times a day. Intravenous administration of acyclovir was incidentally discontinued and changed to oral administration of acyclovir when he suddenly developed a seizure-like symptom ten days after hospitalization.

His stromal edema began to resolve steadily after the initiation of the regimen in the hospital and had completely subsided two months later (Fig. 1, middle right and left). At this time, his best-corrected visual acuity was improved to 20/20 in the left eye. On Feb. 4, 1990, he was discharged from the hospital and instructed to use topically applied acyclovir and corticosteroid eyedrops for one month. Oral administration of acyclovir was discontinued on the same day. When he came back to our clinic on March 10, 1990, the endothelial lesion was relapsed in the same eye. Prominent stromal edema was again observed at the lower part of the cornea (Fig. 1, bottom right and left). The number of keratic precipitates lining the edge of the stromal edema had increased. Satellite lesions were observed at the upper half of the cornea. On inquiry, he said that he had not used topically applied acyclovir as instructed. Therefore, we resumed the former treatment regimen consisting of topical application and oral administration of acyclovir combined with corticosteroid eyedrops. An aliquot of the aqueous humor was also aspirated for polymerase chain reaction.

With this treatment, his stromal edema started to resolve and had completely subsided one month later. The lesion has not recurred since then. On June 19, 1990, he came back to us with a complaint of intolerable ocular pain. Slit-lamp examination disclosed large epithelial bullae formation in the center of the cornea, indicating endothelial decompensation. The endothelial lesions did not recur. Because he had no ocular irritation, he had been using extended-wear soft contact lenses. His best-corrected visual acuity was 20/60 in the left eye on March 12, 1991.

Serum antibody titers (IgG and IgM) were examined using an immunofluorescent method once on Nov. 3 and once on 28, 1989.

At the first examination, immunofluorescent antibody titers were 1:160 (IgG) and below 1:10 (IgM) for herpes simplex virus, 1:160 (IgG) and below 1:10 (IgM) for herpes zoster virus, and 1:160 (IgG) and below 1:10 (IgM) for cytomegalovirus. At the second examination, there was no marked change in antibody titer to any virus. Thus, immunofluorescent antibody titers were 1:80 (IgG) and below 1:10 (IgM) for herpes simplex virus, 1:160 (IgG) and below 1:10 (IgM) for herpes zoster virus, and 1:160 (IgG) and below 1:10 (IgM) for cytomegalovirus.

Virus isolation was attempted by using the aqueous humor that had been obtained at the first exacerbation. An aliquot of the aqueous humor was inoculated onto human embryonic lung fibroblasts (MRS-5). Virus was not isolated after a four-week incubation at 37 C.

The obtained aqueous humor was incubated at 55 C for one hour in a final reaction volume of 500 μl containing 100 μg of proteinase K per ml, 0.5% sodium dodecyl sulfate, 1mM EDTA, and 10mM Tris-HCl (pH 7.8). After tRNA was added as a carrier, the reactant was then phenol-chloroform extracted, and precipitated for DNA with ethanol. The precipitate was finally dissolved in 50 μl of Tris-EDTA buffer (10mM Tris-HCl, pH 7.5, 1mM EDTA).

To amplify herpes simplex virus or herpes zoster virus DNA, a polymerase chain-reaction procedure was performed according to the method described by Saiki and associates.[9] In brief, 10 μl of treated samples were subjected to polymerase chain reaction in 100 μl of polymerase chain-reaction buffer (10mM Tris-HCl, pH 8.3, 50mM KCl, 1.5mM MgCl$_2$, 0.01% gelatin) in the presence of 80 μM deoxynucleotide triphosphate (dATP, dGTP, dCTP, or dTTP), 20 pM each of 5′ and 3′ primers, and 2.5 μM of *Thermus aquaticus* DNA polymerase. A pair of primers that bracketed a 92–base pair segment of the DNA polymerase (Research Genetics, Huntsville, Alabama) was used for herpes simplex virus. A pair of primers that bracketed a 1-K base pair segment of the thymidine kinase was also used for herpes zoster virus. Their sequences were as follows:

5′ATGTCAACGGATAAAACCGATGTAA and
5′ GGAAGTGTTGTCCTGAACGGG.

After being laid over by 50 μl of mineral oil, the mixture was placed in a thermal cycler (Cetus, Perkins-Elmer, Norwalk, Connecticut). The sample was then heated at 94 C for 30 seconds for denaturation, then cooled at 55 C for 30 seconds for annealing, and incubated at 72 C for 30 seconds for elongation. This cycle was repeated 30 times. Sensitivity of our polymerase chain reaction was 0.01 plaque-forming units/ml.

After DNA amplification, a 10-μl aliquot of the reaction mixture was subjected to gel electrophoresis on 4% agarose in Tris-borate-EDTA buffer, and stained with ethidium bromide for visualization by ultraviolet fluorescence. The specificity of the amplified band was confirmed by the Southern blot hybridization technique, using a ^{32}P-labeled probe.

The amplified bands of appropriate sizes were demonstrated in lanes 1 and 2 in which polymerase chain-reaction products for herpes simplex virus performed on DNA extracted from the patient's aqueous humor were applied. The autoradiographic profile of Southern blot analysis reconfirmed that these amplified bands were specific for herpes simplex virus (Fig. 2, right). Deoxyribonucleic acid amplification of the aqueous humor for herpes zoster virus was negative.

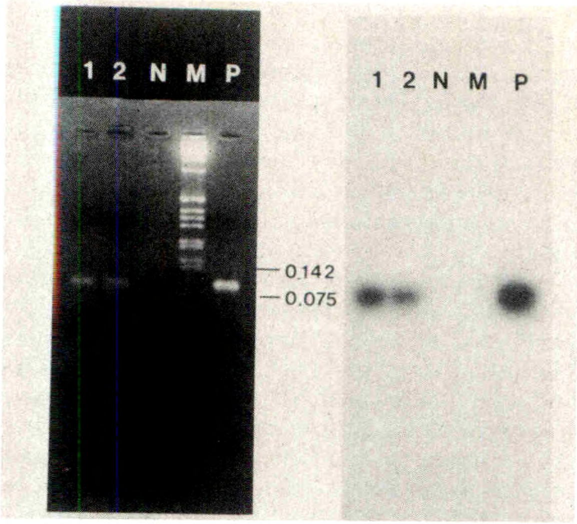

Fig. 2 (Ohashi and associates). Left, Gel-electrophoretic profiles of polymerase chain reaction for herpes simplex virus. Right, Autoradiophotographs showing Southern immunoblot analysis of DNA products amplified for herpes simplex virus. 1 indicates the aqueous humor at the first exacerbation, 2 indicates the aqueous humor at the second exacerbation, N indicates negative control for the assay, M indicates molecular markers, and P indicates positive control for herpes simplex virus. The numbers indicate the size in base pairs of molecular standards.

Discussion

Our study clearly demonstrates that the unique endothelial disorder, designated idiopathic corneal endotheliopathy, is caused by herpes simplex virus. Our patient fulfilled several clinical characteristics of this particular disease, which have been described in previous reports.[1-8] Progressively advancing corneal stromal edema that started from the periphery and numerous postkeratic precipitates closely associated with the edema constitute hallmarks of this disease. Idiopathic corneal endotheliopathy can be easily distinguished from herpetic disciform keratitis according to the following characteristics: (1) peripheral location of stromal edema; (2) lack of cellular infiltrates in the stroma including an immune ring; and (3) minimum degree of ciliary injection.

Lines of evidence can be linked to the viral infection hypothesis of origin. First, using a polymerase chain-reaction technique, herpes simplex virus–specific DNA was demonstrated in the patient's aqueous humor that was obtained at the first exacerbation. The amplified band for herpes simplex virus was repeatedly demonstrated at the next exacerbation. This suggests the viral infection as the pathogenetic mechanism of this disease. It may be that this infection resulted from the incidental shedding of herpes simplex virus into the aqueous humor that was unrelated to the disease itself. This is unlikely, however, because no amplified herpes simplex virus DNA was demonstrable in the aqueous humor from patients undergoing cataract operations (our unpublished data).

Secondly, the endothelial lesion was rapidly resolved in response to topically applied and systemic acyclovir treatment. Similar efficacy of topical antiherpetic agents has been reported previously.[2,6] This clinical observation at least suggests that this disease is caused by an acyclovir-sensitive agent, of which herpes simplex virus is a candidate. Maudgal and associates,[2] two years before Khodadoust and Attarzadeh, reported a case of corneal endotheliitis caused by varicella-zoster virus. Corticosteroid eyedrops were seemingly effective in reducing stromal edema during the first two weeks. However, its efficacy was eventually incomplete. The autoimmune theory, therefore, may not be applicable to our case.

It may not be possible to exclude the autoimmune theory because no infective virus was isolated from the aqueous humor. However, it is also reasonable to consider that the viral proliferation in the corneal endothelium was too low to be detected by a routine examination technique. Although this disease may sometimes develop via the autoimmune mechanism as proposed by Khodadoust and Attarzadeh,[1] there is much more evidence that supports the viral origin.

The origin of the herpes simplex virus and how it could infect the corneal endothelium was questioned in our case. It is speculated that the herpes simplex virus might be secreted from the trabeculum, having been triggered by a long-term immunosuppression with prednisolone and cyclophosphamide. This reaction is possible because the corneal stromal edema usually begins from the periphery, intraocular pressure often increases in a patient who has this disease, and the trabecular meshwork is innervated by the trigeminal nerve by which a herpes simplex virus travels up and down.[10] It may also be postulated that idiopathic corneal endotheliopathy is caused by a variant of herpes simplex virus or herpes zoster virus with a high affinity for the corneal endothelium. Virus-induced corneal endotheliopathy may suddenly emerge as a prevalent disease caused by herpes simplex virus or herpes zoster virus,[11] as has acute retinal necrosis in the last two decades.

References

1. Khodadoust, A. A., and Attarzadeh, A.: Presumed autoimmune corneal endotheliopathy. Am. J. Ophthalmol. 93:718, 1982.

2. Maudgal, P. C., Missotten, L., DeClercq, E., and Descamps, J.: Varicella-zoster virus in the human corneal endothelium. A case report. Bull. Soc. Belge Ophtalmol. 190:71, 1980.

3. Sugar, A., and Smith, T.: Presumed autoimmune corneal endotheliopathy. Correspondence. Am. J. Ophthalmol. 94:689, 1982.

4. Sutcliffe, E., and Baum, J.: Acute idiopathic corneal endotheliitis. Ophthalmology 91:1161, 1984.

5. Ohashi, Y., Kinoshita, S., Mano, T., Kiritoshi, A., and Ohji, M.: Idiopathic corneal endotheliopathy. A report of two cases. Arch. Ophthalmol. 103:1666, 1985.

6. Robin, J. B., Steigner, J. B., and Kaufman, H. E.: Progressive herpetic corneal endotheliitis. Am. J. Ophthalmol. 100:336, 1985.

7. Kuljaca, Z. D., and Momirov, D. M.: Idiopathic sectorial corneal endotheliitis. Am. J. Ophthalmol. 99:728, 1985.

8. Khodadoust, A. A., Karnama, Y., Stoessel, K. M., and Puklin, J. E.: Pars planitis and autoimmune endotheliopathy. Am. J. Ophthalmol. 102:633, 1986.

9. Saiki, R. K., Gelfand, D. H., Stoffel, S., Sharf, S. J., Higuchi, R., Horn, G. T., Mullis, K. B., and Erlich, H. A.: Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. Science 239:487, 1988.

10. Stone, R. A., and Kuwayama, Y.: Substance P-like immunoreactive nerves in the human eye. Arch. Ophthalmol. 103:1207, 1985.

11. Culbertson, W. W.: Varicella zoster is a cause of acute retinal necrosis. Ophthalmology 93:296, 1986.

The Effects of Denatured Sodium Hyaluronate on the Corneal Endothelium in Cats

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In an in vivo cat model, wide-field specular microscopy and scanning electron microscopy were used to observe whether heat-denatured sodium hyaluronate causes cell damage to the corneal endothelium. The endothelial cell toxicities of various drugs, including 0.01% benzalkonium chloride, 0.2% chlorhexidine digluconate, and 0.5% lidocaine, mixed with intact or untreated sodium hyaluronate were also investigated. Neither heat-denatured nor intact or untreated sodium hyaluronate alone had any adverse effect on the corneal endothelium in cats, whereas 0.01% benzalkonium chloride and 0.2% chlorhexidine digluconate, mixed with sodium hyaluronate, caused substantial endothelial morphologic changes, which resulted in corneal edema.

By comparison, 0.5% lidocaine with sodium hyaluronate was found to have minimal effect on the corneal endothelium in cats. These findings indicate that some chemical contaminant with sodium hyaluronate, not heat-denatured sodium hyaluronate, induces an immediate onset of pseudophakic bullous keratopathy.

PSEUDOPHAKIC BULLOUS KERATOPATHY is one of the most serious complications after intraocular lens implantation. Although it has been reported that the incidence of pseudophakic bullous keratopathy with posterior chamber lens implantation was lower than that associated with iris-fixated or anterior chamber lenses,[1-3] Lugo and associates[4] found that the incidence of pseudophakic bullous keratopathy has been increasing in patients with posterior chamber lens implants. Previous studies note that pseudophakic bullous keratopathy related to posterior chamber lenses exhibited earlier onset of corneal edema, in comparison with cases involving iris-fixated and anterior chamber lenses.[5-8] For example, some reports describe the onset of corneal edema as developing in a range from immediately through several months after surgery.[1-5]

Several studies suggest that preexisting endothelial dystrophy may be a considerable contributing factor in the early development of corneal decompensation after posterior chamber lens implant.[1,4,5] However, acute onset of bullous keratopathy has been reported in patients undergoing posterior chamber lens implantation, despite the absence of surgical complications or preexisting endothelial dystrophy.[1,9,10] Kim[9] proposed that corneal decompensation may be caused by sodium hyaluronate denatured by autoclaving or sterilizing materials that were injected into the anterior chamber, although there has been no scientific evidence to prove this. Moreover, Breebaart and associates[10] recently speculated that a detergent for the cleaning of surgical instruments was a suspect material.

Because sodium hyaluronate has been extensively used as a viscous material for anterior segment procedures, denatured sodium hyaluronate's potential for damaging the corneal endothelium required experimental evaluation. Therefore, we investigated in vivo the toxic effect of denatured sodium hyaluronate on the corneal endothelium in cats, which has limited proliferative potential, as does the human corneal endothelium.

Material and Methods

The use of animals in the current study conformed to the Association for Research in Vi-

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sion and Ophthalmology Resolution on the Use of Animals in Research.

Twenty eyes of ten European, approximately 4-kg cats were used in this study. These eyes were randomly and equally divided into the following five groups, according to the drugs tested: Group A, intact or untreated sodium hyaluronate (molecular weight, 1,200,000; Santen Pharmaceutical Co. Ltd., Osaka, Japan); Group B, sodium hyaluronate denatured by autoclaving (at 121 C for 20 minutes); Group C, normal sodium hyaluronate mixed with 0.01% benzalkonium chloride (4:1 v/v); Group D, intact or untreated sodium hyaluronate mixed with 0.2% chlorhexidine digluconate (4:1 v/v); Group E, intact or untreated sodium hyaluronate mixed with 0.5% lidocaine (4:1 v/v).

After each cat was anesthetized with intramuscular injection of ketamine hydrochloride (30 mg/kg of body weight), 27-gauge bent needles with 1-ml disposable cylinders were introduced into the anterior chamber at the three and nine o'clock positions on the surgical corneoscleral limbus, away from both iris and corneal endothelium. Each test drug (0.25 ml) was then introduced into the anterior chamber via the cylinder at the nine o'clock position. At the same time, 0.25 ml of aqueous humor was aspirated via the cylinder at the three o'clock position, to keep intraocular pressure constant.

All eyes were examined via slit-lamp biomicroscopy and wide-field specular microscopy of the central corneal endothelium before and one, four, and seven days after drug delivery. Specular microscopic examination in Group C after one and four days could not be performed because of severe corneal edema. The degree of corneal edema was clinically evaluated by using the criteria reported by Draize, Woodard, and Calvery.[11] For specular microscopic analysis, 100 endothelial cells in the best two photographs were traced and analyzed with a computer-assisted digitizer as described previously.[12,13] After all eyes were enucleated seven days after surgery and fixed in 2.5% glutaraldehyde, the corneal endothelium was examined by scanning electron microscopy. The two-tailed, paired *t*-test was used for statistical analysis.

Results

Clinical observations—Neither Group A nor Group B showed corneal edema or anterior chamber reaction throughout the observation periods. Conversely, severe corneal edema with anterior chamber inflammation developed immediately and up to four days after drug delivery in all four eyes in Group C. The stromal edema was more profound in the nine o'clock position than it was in the central cornea. This edema decreased with time. Corneal edema also followed this pattern in Group D; however, it was milder than that in Group C. Group E showed far milder edema than did either Group C or D (Table 1).

Specular microscopic analysis—The baseline variables of all five groups were equivalent, including central corneal endothelial cell density, coefficient of variation in cell size, and percentage of hexagonal cells. Throughout the observation period, the percentage of corneal endothelial cell loss, coefficient of variation, or percentage of hexagonal endothelial cells in Groups A and B did not differ significantly.

In Group C, the corneal endothelium showed marked cell loss, marked increase in coefficient of variation, and marked decrease in hexagonal cells after seven days. In Group D, the corneal endothelium showed a statistically significant increase in the coefficient of variation after one day ($P = .0324$) and seven days ($P = .0324$). Although 7% cell loss was observed at seven days and hexagonal cells decreased slightly, these changes were not statistically significant. In Group E, percentage of cell loss, coefficient of variation, or percentage of hexagonal cells did not change significantly throughout the observation period, although the percentage of hexagonal cells tended to decrease at seven days (Table 2).

Scanning electron microscopy—The morphologic appearance of the corneal endothelium in Groups A and B was within the normal range, both at the center and near the nine o'clock position (Fig. 1). Conversely, a majority of the endothelial cells in the area near the nine o'clock position were destroyed, and fibroblasts and newly generated membranous tissues covered the denuded Descemet's membrane in Group C. The corneal endothelium in the center showed monolayer cells with marked polymegethism and pleomorphism. In Group D, both polymegethism and pleomorphism in the corneal endothelium were marked near the nine o'clock position, but were moderate in the center. Cell size increased by about 10%. In Group E, the corneal endothelium was almost normal in appearance in the area near the nine o'clock position and at the center (Fig. 2).

TABLE 1
CLINICAL SEVERITY OF CORNEAL EDEMA

GROUP	OBSERVED AREA	CLINICAL SCORE OF CORNEAL EDEMA* ONE DAY AFTER DRUG DELIVERY	FOUR DAYS AFTER DRUG DELIVERY	SEVEN DAYS AFTER DRUG DELIVERY
Group A	Center	0	0	0
(N = 4)	Nine o'clock position	0	0	0
Group B	Center	0	0	0
(N = 4)	Nine o'clock position	0	0	0
Group C	Center	3.0	2.3	2.0
(N = 4)	Nine o'clock position	4.0	4.0	3.3
Group D	Center	2.5	1.8	1.0
(N = 4)	Nine o'clock position	3.3	3.0	2.3
Group E	Center	1.0	0.8	0
(N = 4)	Nine o'clock position	1.8	1.3	0.8

*Clinical score number indicates average value. Clinical scoring of corneal edema: 0, no opacity; 1, a scattered or diffuse area is present, but details of iris clearly visible; 2, an easily discernible translucent area, but details of iris slightly obscured; 3, an opalescent area with no visible details of iris or pupil; and 4, opaque cornea and invisible iris.

TABLE 2
SPECULAR MICROSCOPIC DATA OF CORNEAL ENDOTHELIUM (N = 4)

VARIABLES*	GROUP	BEFORE SURGERY	ONE DAY AFTER SURGERY	FOUR DAYS AFTER SURGERY	SEVEN DAYS AFTER SURGERY
Cell loss (%)	A	—	1.0 ± 1.1	0.0 ± 1.8	−2.0 ± 1.9
	B	—	0.0 ± 0.9	2.0 ± 1.1	−1.0 ± 0.9
	C	—	—	—	30.9 ± 4.4[†]
	D	—	−3.8 ± 7.6	6.4 ± 11.7	7.1 ± 15.0
	E	—	−2.0 ± 2.8	−3.1 ± 3.0	1.0 ± 2.7
Coefficient of variation	A	0.15 ± 0.01	0.14 ± 0.01	0.15 ± 0.01	0.16 ± 0.02
	B	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.14 ± 0.01
	C	0.14 ± 0.02	—	—	0.56 ± 0.04[‡]
	D	0.14 ± 0.02	0.18 ± 0.03[§]	0.17 ± 0.02	0.18 ± 0.01[‖]
	E	0.15 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.02
Hexagons (%)	A	68.9 ± 2.8	67.7 ± 2.6	71.7 ± 5.5	71.0 ± 9.7
	B	70.2 ± 2.7	71.2 ± 9.5	70.2 ± 3.1	73.5 ± 8.0
	C	68.2 ± 4.1	—	—	39.7 ± 8.8[#]
	D	69.6 ± 6.9	60.8 ± 14.1	66.4 ± 6.5	66.4 ± 6.3
	E	75.4 ± 2.1	71.0 ± 4.1	71.4 ± 4.6	64.6 ± 2.7

*Each value indicates mean ± standard deviation of eyes.

[†] Preoperative and postoperative values significantly different (P = .0008).

[‡] Preoperative and postoperative values significantly different (P = .0007).

[§] Preoperative and postoperative values significantly different (P = .0374).

[‖] Preoperative and postoperative values significantly different (P = .0324).

[#] Preoperative and postoperative values significantly different (P = .0096).

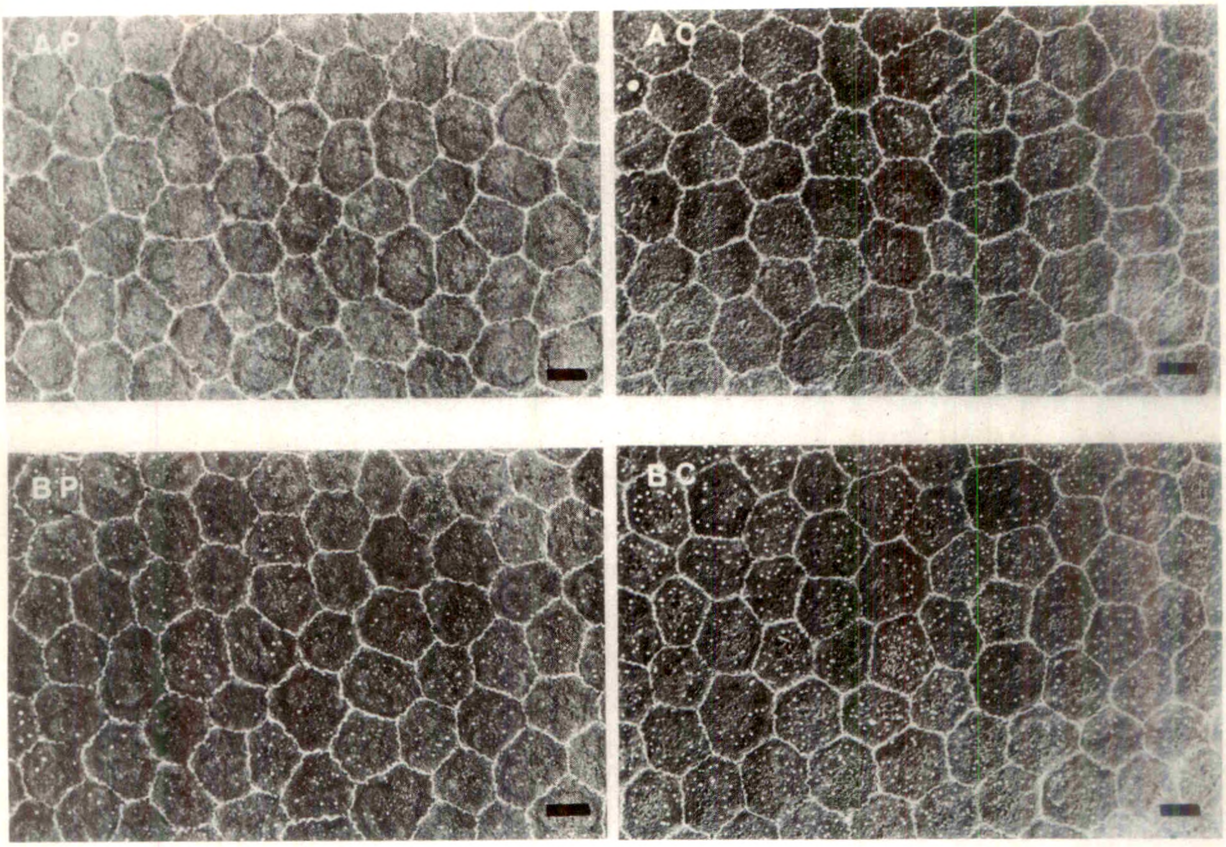

Fig. 1 (Ohguro, Matsuda, and Kinoshita). Scanning electron micrographs of corneal endothelia exposed to either 1% normal sodium hyaluronate or heat-denatured sodium hyaluronate. AP indicates the area near the nine o'clock position in Group A, AC indicates the center in Group A, BP indicates the area near the nine o'clock position in Group B, and BC indicates the center in Group B. Bar indicates 10 μm.

Discussion

Our study clearly demonstrates that sodium hyaluronate denatured by autoclaving has no toxic effect on corneal endothelium. Although heat-denatured sodium hyaluronate may show some physiochemical alteration, it is safe enough to be applied to the anterior chamber.

Conversely, sodium hyaluronate mixed with benzalkonium chloride shows remarkable endothelial cell toxicity, as previously reported.[14-16] Accidental inclusion of benzalkonium chloride with sodium hyaluronate, however, seems to be extremely uncommon at the time of surgery.

As previously suggested,[17] sodium hyaluronate with 0.2% chlorhexidine digluconate also showed endothelial cell toxicity near the area where the drug was injected and the central cornea, although the degree of damage was greater in the injected area than it was in the center. Because chlorhexidine digluconate has sometimes been used as a sterilizing solution for surgical instruments in ophthalmic surgery (as have both autoclaving and ethylene oxide gas sterilization) in Japan as well as in developing countries, accidental contamination with chlorhexidine digluconate might cause pseudophakic bullous keratopathy in intraocular lens surgery. In our study, sodium hyaluronate with 0.5% lidocaine also slightly damaged the corneal endothelium, although its toxicity is probably not sufficient to cause acute onset of pseudophakic bullous keratopathy. Previous reports indicate that the corneal endothelium is also damaged by several other drugs, such as epinephrine,[18-20] beta-blocker,[21-23] and thrombin.[24] However, because these drugs show an endothelial cell toxicity as mild as that of lidocaine, it is reasonable to eliminate them as causative drugs in the acute onset of pseudophakic bullous keratopathy.

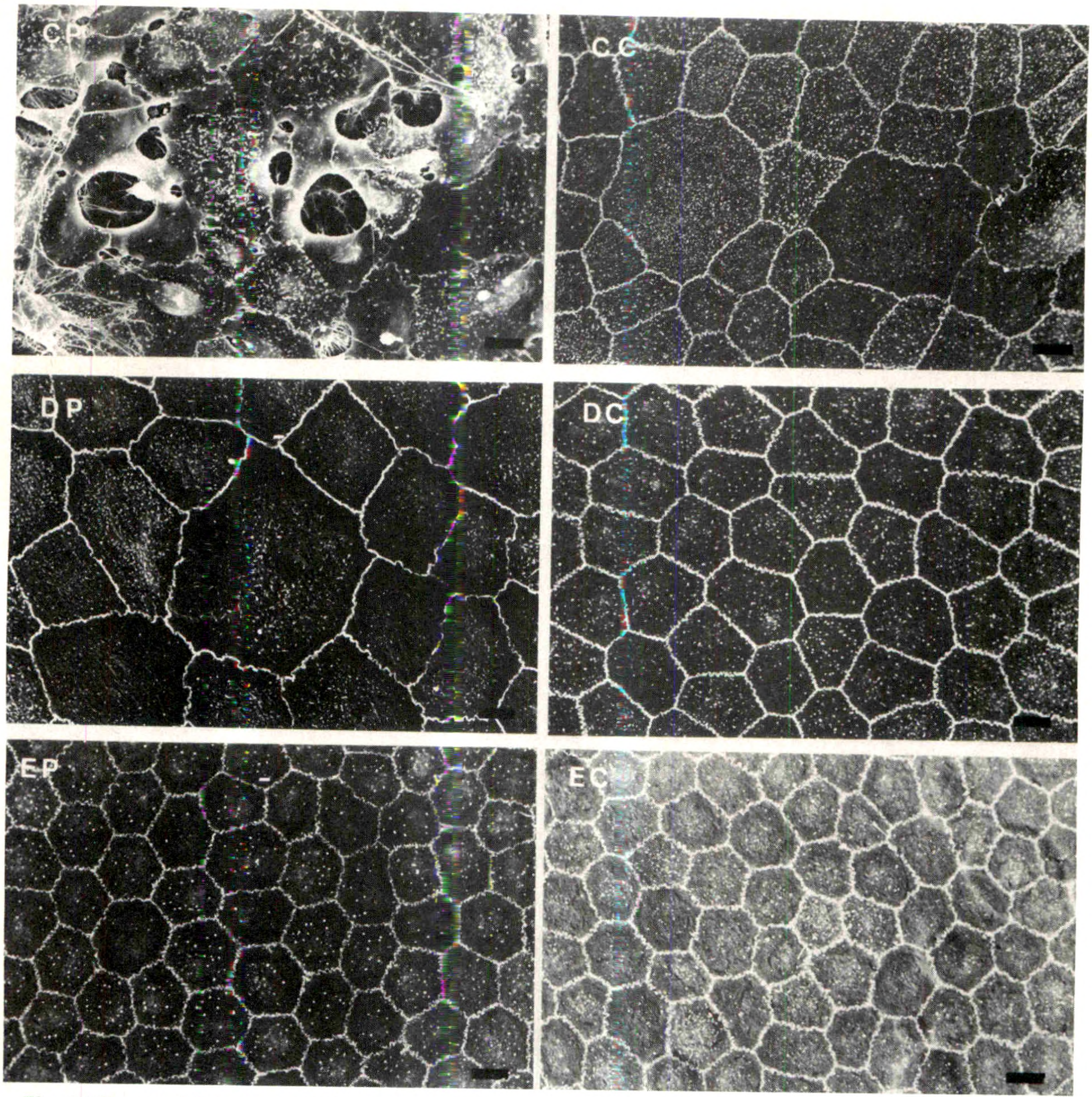

Fig. 2 (Ohguro, Matsuda, and Kinoshita). Scanning electron micrographs of corneal endothelia exposed to sodium hyaluronate mixed with 0.01% benzalkonium chloride, 0.2% chlorhexidine digluconate, or 0.5% lidocaine. CP indicates the area near the nine o'clock position in Group C, CC indicates the center in Group C, DP indicates the area near the nine o'clock position in Group D, DC indicates the center in Group D, EP indicates the area near the nine o'clock position in Group E, and CC indicates the center in Group E. Bar indicates 10 μm.

Our findings support the concept that acute onset of pseudophakic bullous keratopathy (presently named toxic endothelial cell dysfunction[10]) is probably caused by drug contamination of sodium hyaluronate (contamination with chlorhexidine digluconate, for example). Nuyts and associates[25] also demonstrated recently that marked corneal endothelial damage occurred when residue of a nonionic ethoxylated fatty alcohol, one component in detergent material, was introduced into the anterior chamber from an irrigating cannula. They strongly suspected that a detergent solution in the cannula was the causative agent. Therefore, it is quite possible that acute onset of pseudophakic bullous keratopathy could happen via an irrigating cannula that has been contaminated by either sterilizing solution, as postulated in our study, or by cleaning solution, as suggested by Breebaart and associates[10] and Nuyts and associates,[25] at the surgery set-up procedure. To protect against accidental contamination with sodium hyaluronate or other irrigating fluids, the use of disposable cannulas is essential.

Of additional interest in our study is that corneal endothelial cells near the drug-injection area were more severely damaged than those in the central region. The different toxicity in the two areas may be because of the different drug concentration induced by drug diffusion or simply because of mechanical damage. Because sodium hyaluronate is a strongly hydrophilic substance, it has high affinity for such chemicals as chlorhexidine digluconate and benzalkonium chloride, and drug clearance from the anterior chamber can be delayed. Therefore, it is possible that a toxic substance mixed with high-molecular weight sodium hyaluronate may show more severe endothelial cell damage than would the drug alone. There is also a possibility that the hyaluronate-acid binding site on the corneal endothelium[26] may influence the degree of drug toxicity when a toxic solution in sodium hyaluronate is introduced into the anterior chamber.

References

1. Koenig, B. S., and Schultz, R. O.: Penetrating keratoplasty for pseudophakic bullous keratopathy after extracapsular cataract extraction. Am. J. Ophthalmol. 105:348, 1988.

2. Taylor, D. M., Atlas, B. F., Romanchuck, K. G., and Stern, A. L.: Pseudophakic bullous keratopathy. Ophthalmology 90:19, 1983.

3. Berkowitz, P., Orton, R. B., Boyaner, D., and Brownstein, S.: Pseudophakic bullous keratopathy. A clinical-pathologic analysis. Can. J. Ophthalmol. 14:3, 1979.

4. Lugo, M., Cohen, E. J., Eagle, R. C., Paker, A. V., Laibson, P. R., and Arentsen, J. J.: The incidence of preoperative endothelial dystrophy in pseudophakic bullous keratopathy. Ophthalmic Surg. 19:16, 1988.

5. Cohen, E. J., Brady, S. E., Leavitt, K., Lugo, M., Speaker, M. G., Laibson, P. R., and Arentsen, J. J.: Pseudophakic bullous keratopathy. Am. J. Ophthalmol. 106:264, 1988.

6. Sugar, J., Wiet, P. S., and Meisler, M. D.: Pseudophakic bullous keratopathy with intermedics model 024 (Hessburg) anterior chamber intraocular lenses. Arch. Ophthalmol. 106:1575, 1988.

7. Smith, P. W., Wong, S. K., Stark, W. J., Gottsh, J. D., Terry, A. C., and Bonham, R. D.: Complications of semiflexible closed anterior chamber intraocular lenses. Arch. Ophthalmol. 105:52, 1987.

8. Arentsen, J. J., Donoso, R., Laibson, P. R., and Cohen, E. J.: Penetrating keratoplasty for the treatment of pseudophakic corneal edema associated with posterior chamber lens implantation. Ophthalmic Surg. 18:514, 1987.

9. Kim, H. J.: Intraocular inflammation of denatured viscoelastic substance in cases of cataract extraction and lens implantation. J. Cataract Refract. Surg. 13:537, 1987.

10. Breebaart, A. C., Nuyts, R. M., Pels, E., Edelhauser, H. F., and Verbraak, F. D.: Toxic endothelial cell destruction of the cornea after routine extracapsular cataract surgery. Arch. Ophthalmol. 108:1121, 1990.

11. Draize, J. H., Woodard, J., and Calvery, H. O.: Method for the study of irritation and toxicity of substances applied topically to skin and mucous membranes. J. Pharmacol. Exp. Ther. 82:377, 1944.

12. Schultz, R. O., Matsuda, M., Yee, R. W., Edelhauser, H. F., and Schultz, K. J.: Corneal endothelial changes in type I and type II diabetes mellitus. Am. J. Ophthalmol. 98:401, 1984.

13. Yee, R. W., Matsuda, M., Schultz, R. O., and Edelhauser, H. F.: Changes in the normal corneal endothelial cellular pattern as a function of age. Curr. Eye Res. 6:671, 1985.

14. Gasset, A. R., Ishii, Y., Kaufman, H. E., and Miller, T.: Cytotoxicity of ophthalmic preservatives. Am. J. Ophthalmol. 78:98, 1974.

15. Green, K., Hull, D. S., Veughu, E. D., Malizia, A. A., and Bowman, K.: Rabbit endothelial response to ophthalmic preservatives. Arch. Ophthalmol. 95:2218, 1977.

16. Lemp, M. A., and Zimmerman, L. E.: Toxic endothelial degeneration in ocular surface disease treated with topical medications containing benzalkonium chloride. Am. J. Ophthalmol. 105:670, 1988.

17. Green, K., Livingstone, V., Bowman, K., and Hull, D. S.: Chlorhexidine effects on corneal epithelium and endothelium. Arch. Ophthalmol. 98:1273, 1980.

18. Waltman, S. R., Yarian, D., Hart, W., and Becker, B.: Corneal endothelial changes with long-term topical epinephrine therapy. Arch. Ophthalmol. 95:1357, 1977.

19. Edelhauser, H. F., Hyndiuk, R. A., Zeeb, A., and Schultz, R. O.: Corneal edema and the intraocular use of epinephrine. Am. J. Ophthalmol. 93:327, 1982.

20. Cohen, K. L., van Horn, D. L., Edelhauser, H. F., and Schultz, R. O.: Effect of phenylephrine on normal and regenerated endothelial cells in cat cornea. Invest. Ophthalmol. Vis. Sci. 18:242, 1979.

21. Brubaker, R. F., Coaks, R. L., and Bourne, W. M.: Effect of timolol on the permeability of corneal endothelium. Ophthalmology 86:108, 1979.

22. Staatz, W. D., Radius, R. L., van Horn, D. L., and Schultz, R. O.: Effects of timolol on bovine corneal endothelial culture. Arch. Ophthalmol. 99:660, 1981.

23. Matsuda, M., Ishii, Y., Awata, T., and Fukuda, M.: The effect of long-term topical administration of commercial beta-blockers on the rat corneal endothelium. Int. Ophthalmol. 13:67, 1989.

24. McDermott, M. L., Edelhauser, H. F., and Mannis, M. J.: Intracameral thrombin and the corneal endothelium. Am. J. Ophthalmol. 106:414, 1988.

25. Nuyts, R. M. M., Edelhauser, H. F., Pels, E., and Breebaart, A. C.: Toxic effects of detergents on the corneal endothelium. Arch. Ophthalmol. 108:1158, 1990.

26. Madsen, K., Schenholm, M., Janke, G., and Tengblad, A.: Hyaluronate binding to intact corneas and cultured endothelial cells. Invest. Ophthalmol. Vis. Sci. 30:2132, 1989.

OPHTHALMIC MINIATURE

Davis suffered from neuralgia, the doctors called it, a kind of total seizure of nerves resulting in migraine headaches, nausea, and failing eyesight, which sometimes left him bedridden for weeks at a time. But he held himself ramrod straight when he walked, concealing whatever pain he had. His angular face was now severely drawn, and his lips were tightly compressed. His one good eye gave him the visage of an angry Cyclops, a "cruel wizard look." This was not a man to be trifled with.

Eli N. Evans, *Judah P. Benjamin, The Jewish Confederate*
New York, Macmillan Inc., 1988, p. 127

Evaluation of Dacryocystorhinostomy Failure With Computed Tomography and Computed Tomographic Dacryocystography

Herbert J. Glatt, M.D., Alex C. Chan, M.D., and Lynn Barrett, M.D.

Five patients with dacryocystorhinostomy failures were examined with computed tomography or computed tomographic dacryocystography. In computed tomographic dacryocystography, radiopaque dye was instilled into the lacrimal sac before computed tomography to show its shape, location, and relation to surrounding structures. Problems with the bony ostium were detected in all five patients. Recurrent nasal polyposis, a retained metallic clip, and an unresected ethmoid air cell were also identified. Computed tomography and computed tomographic dacryocystography provided important information that facilitated reoperation after dacryocystorhinostomy failure.

IDENTIFICATION of the cause of dacryocystorhinostomy failure is essential in determining appropriate treatment. In the preoperative evaluation of these cases, the usual physical examination is sometimes supplemented by additional studies such as dacryocystography,[1-3] endoscopy,[4] and computed tomography.[3,5-8]

The combination of dacryocystography and computed tomography has been called computed tomographic dacryocystography.[9] In this study, dacryocystorhinostomy failure was evaluated by computed tomography or computed tomographic dacryocystography.

Material and Methods

Patient population—Five consecutive patients referred after unsuccessful dacryocystorhinostomies by other physicians underwent a comprehensive examination that included slit-lamp examination, basic tear-secretion measurement, assessment of eyelid position and tone, nasal examination, and canalicular probing and lacrimal irrigation when possible.

Radiologic techniques—Two patients were examined with computed tomography. In the face-down position, direct coronal computed tomography was performed with 3-mm contiguous cuts in the region of the lacrimal outflow tract. In the face-up position, axial computed tomography was performed with 3-mm contiguous cuts. Three patients were examined with computed tomographic dacryocystography. This technique was first performed in Case 2 and subsequently performed in all cases with patent canaliculi (Cases 3 and 5). A 22-gauge intravenous catheter was inserted into the lower canaliculus and a radiopaque agent (Pantopaque, Alcon, Inc., Humacao, Puerto Rico) was then injected into the lacrimal sac. Computed tomography was performed after a delay of approximately 15 minutes in the same manner.

Results

Coronal scans were generally more helpful than axial scans. Bone windows were helpful in assessing the adequacy of the bony ostium. Computed tomography or computed tomographic dacryocystography detected problems

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with the bony ostium in all five patients, including improper location, suboptimal size and bone regrowth. Recurrent nasal polyposis adjacent to the previous ostium was imaged in Case 1. A retained metallic clip was imaged in Case 4. An anterior ethmoid air cell requiring resection was imaged in Case 5. Radiologic findings were confirmed during repeat lacrimal surgery in all five patients.

Case Reports

Case 1

A 28-year-old man underwent bilateral nasal polypectomies for severe nasal polyposis. He subsequently developed left epiphora and chronic dacryocystitis. Fifteen months after the nasal polypectomies, another physician performed a left dacryocystorhinostomy that did not relieve his symptoms. We first examined the patient nine months after the previous dacryocystorhinostomy. Manual pressure on the left lacrimal sac produced copious pus. Irrigation through the left lower canaliculus disclosed a total lacrimal block, with reflux of pus from the upper canaliculus. Extensive nasal polyposis was observed on nasal examination. Computed tomography disclosed severe recurrent polyposis throughout the nasal cavity. The previous dacryocystorhinostomy bony opening was contiguous with the polyps and was too small (Fig. 1).

The patient underwent a combined procedure in which an otorhinolaryngologist performed bilateral nasal polypectomies and one of us, an oculoplastic surgeon (H.J.G.), performed an external dacryocystorhinostomy. Intraoperative inspection confirmed that the osteotomy was too small and therefore, it was enlarged. Three months after surgery, fluid irrigated freely from the canaliculi to the nose. Eight months after surgery, the patient reported that he was free of epiphora and symptoms of dacryocystitis.

Case 2

A 70-year-old woman with right epiphora and chronic dacryocystitis had undergone an unsuccessful right dacryocystorhinostomy by another physician. We first examined the patient four years later. Manual pressure on the right lacrimal sac produced copious pus. Irrigation through the lower canaliculus disclosed a total block with reflux of pus from the upper canaliculus. Computed tomographic dacryocystography disclosed that the previous dacryocystorhinostomy bony opening was inferior to the lacrimal sac.

A repeat external dacryocystorhinostomy was performed. Intraoperative inspection confirmed that the previous bony opening was inferior to the sac and therefore, it was enlarged superiorly. Four months after surgery, the patient was free of epiphora and symptoms of dacryocystitis and fluid irrigated freely from the canaliculi to the nose.

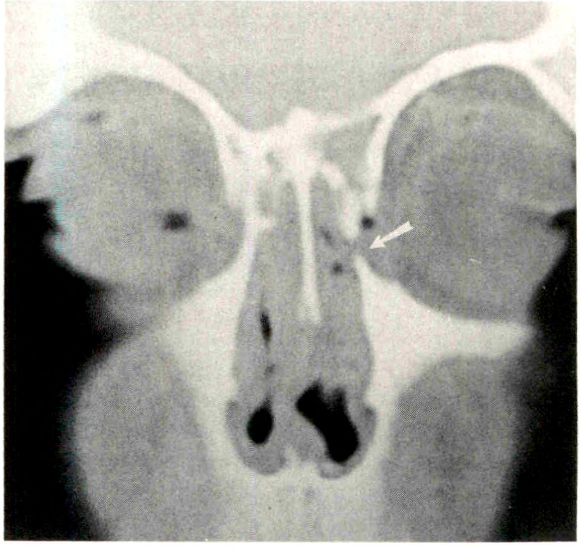

Fig. 1 (Glatt, Chan, and Barrett). Case 1. Coronal computed tomogram of lacrimal obstruction associated with nasal polyposis, previous nasal polypectomy, and not relieved by previous dacryocystorhinostomy. Recurrent nasal polyposis appears on the computed tomogram as soft-tissue densities within the nasal cavity. This contrasts with the air density normally found within the nasal cavity and present in Figures 2 through 4. The osteotomy from the previous dacryocystorhinostomy is too small (arrow). Simultaneous repeat nasal polypectomy and enlargement of the osteotomy was performed.

Case 3

A 32-year-old woman had undergone endoscopic sinus surgery that included bilateral maxillary sinus osteoplasties, nasal septoplasty, bilateral middle turbinectomies, bilateral ethmoidectomies, bilateral infracturing of the inferior turbinates, and partial inferior turbinectomies. She subsequently developed left epiphora and chronic dacryocystitis, presumably because of damage to the left nasolacrimal duct from excessive anterior enlargement of the maxillary sinus ostium.[10] Five months later, an otorhinolaryngologist performed a left dacryo-

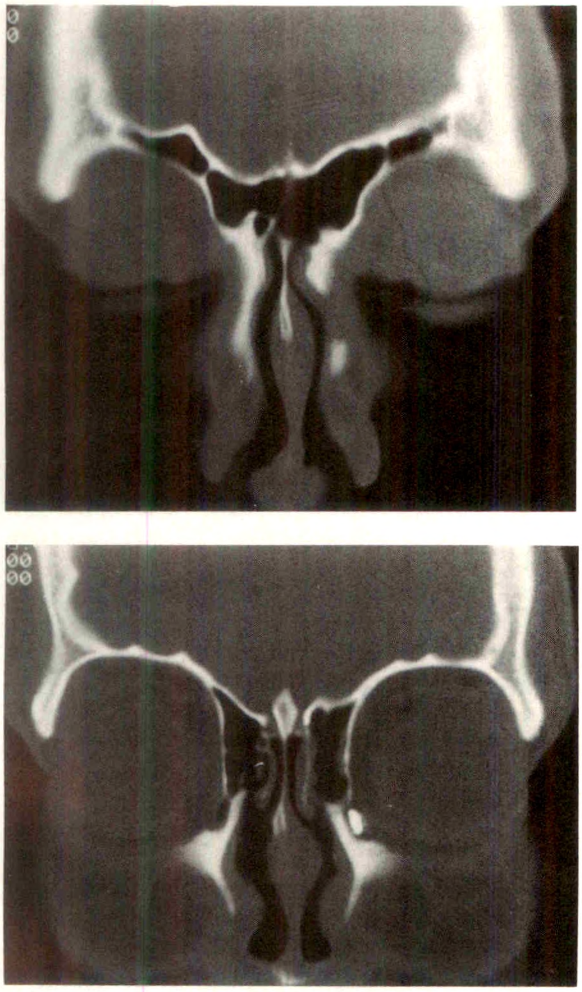

Fig. 2 (Glatt, Chan, and Barrett). Case 3. Coronal computed tomographic dacryocystographic scan of lacrimal obstruction not relieved by previous dacryocystorhinostomy. Radiopaque dye has been instilled in the lacrimal sac. Top, The bony ostium from the previous dacryocystorhinostomy is apparent but no dye is seen because the ostium is anterior to the lacrimal sac. Bottom, A more posterior coronal section discloses dye in the lacrimal sac and bone between the lacrimal sac and the nasal cavity, again indicating that the bony ostium is not posterior enough. Posterior enlargement of the osteotomy was performed during repeat dacryocystorhinostomy.

cystorhinostomy, which did not relieve her symptoms. We first examined the patient 14 months after the previous dacryocystorhinostomy. Irrigation through the left lower canaliculus disclosed total reflux into the conjunctival cul-de-sac through a medial canthal fistula. Computed tomographic dacryocystography disclosed that the previous dacryocystorhinostomy bony opening was anterior to the lacrimal sac (Fig. 2).

A repeat external dacryocystorhinostomy was performed. Intraoperative inspection confirmed that the previous osteotomy was anterior to the lacrimal sac and therefore it was enlarged posteriorly. Four months after surgery, the patient was free of epiphora and symptoms of dacryocystitis and fluid irrigated freely from the canaliculi to the nose.

Case 4

A 13-year-old girl who had epiphora caused by bilateral congenital absence of the canaliculi since early in life had undergone bilateral canalicular reconstruction and dacryocystorhinostomies by another physician, which did not relieve her symptoms. The previous physician stated that the entire bony wall of each lacrimal sac fossa had been removed. We first examined the patient two years later. Obvious bilateral epiphora was present. All four puncta were absent. A firm and uninflamed left lacrimal sac mass was observed. Computed tomography disclosed a mucocele of the left lacrimal sac. Bilateral bone regrowth had apparently developed, which separated the lacrimal sacs from the nasal cavity. A small dense object was detected in the superomedial lacrimal sac (Fig. 3).

A left conjunctival dacryocystorhinostomy with placement of a Jones tube was performed. Intraoperative inspection confirmed that bony regrowth had developed and therefore, a repeat osteotomy was performed. The dense object in the sac proved to be a metallic clip that had been placed around silicone tubing during the previous surgery and had remained in the sac after removal of the tubing. The clip was removed. Six weeks after surgery, she was free of epiphora and the Jones tube was in good position. Surgery on the right is planned.

Case 5

An 80-year-old woman with left chronic dacryocystitis had undergone two unsuccessful left dacryocystorhinostomies. We first examined the patient ten years later. Manual pressure on the left lacrimal sac produced pus. Irrigation through the lower canaliculus disclosed a total block with reflux of pus from the upper canaliculus. Computed tomographic dacryocystography disclosed that the previous dacryocystorhinostomy bony opening was inferior to the lacrimal sac and that an unresected ethmoid air cell was adjacent to the lacrimal sac (Fig. 4).

A repeat dacryocystorhinostomy was performed. Intraoperative inspection confirmed that the previous osteotomy was inferior to the

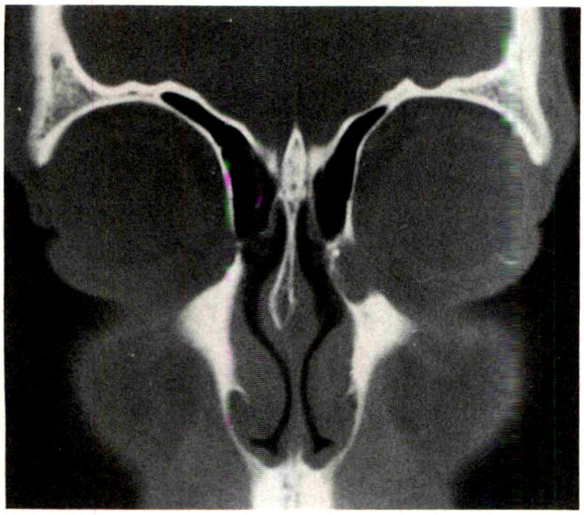

Fig. 3 (Glatt, Chan, and Barrett). Case 4. Coronal computed tomogram of a patient with bilateral congenital absence of the canaliculi who had undergone unsuccessful bilateral canalicular reconstruction and dacryocystorhinostomy. Bilateral bone regrowth has apparently occurred, separating the lacrimal sacs from the nasal cavity. On the left side of the photograph (patient's right), a small bony defect is still present. On the right side of the photograph (patient's left), the lacrimal sac is separated from the nasal cavity by a thin layer of bone. The small round density in the patient's left superomedial sac proved to be a metallic clip.

lacrimal sac and therefore, it was enlarged superiorly. An ethmoid air cell adjacent to the lacrimal sac was resected. Three months after surgery, the patient was free of epiphora and dacryocystitis and fluid irrigated freely from the canaliculi to the nose.

Discussion

Dacryocystorhinostomy failure may result from the following causes[1-8]: (1) ostium; inappropriate size or location, or both, bone regrowth, or soft-tissue regrowth; (2) lacrimal sac; scarring from trauma, previous surgery, nonabsorbable sutures or clips, or inadequate surgical opening; (3) canalicular abnormalities; (4) anatomic variants of nasal cavity or sinuses; anterior ethmoids, anterior middle turbinate, or deviated septum; (5) tumors; lacrimal sac nasal, or sinus; (6) inflammatory diseases; sarcoid or pseudotumor; and (7) epiphora unrelated to lacrimal outflow tract abnormalities.

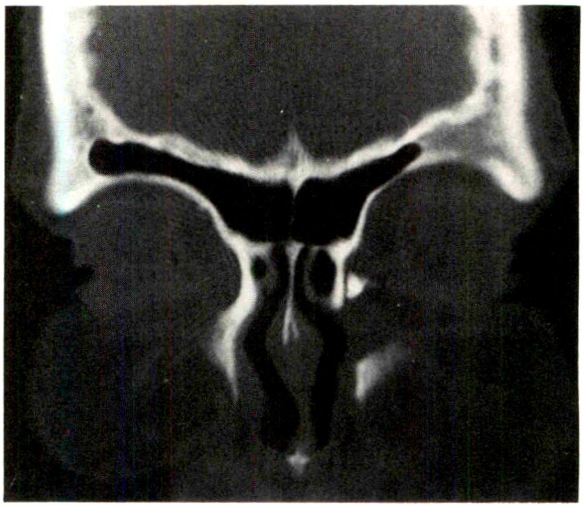

Fig. 4 (Glatt, Chan, and Barrett). Case 5. Coronal computed tomographic dacryocystographic scan of lacrimal obstruction not relieved by two previous dacryocystorhinostomies. Radiopaque dye has been instilled in the lacrimal sac. On the right side of the photograph (patient's left), dye is seen in the lacrimal sac. The ostium from the previous dacryocystorhinostomy is inferior to the sac. The sac is separated from the nasal cavity by the bony wall of the lacrimal sac fossa and an anterior ethmoid air cell. Both had to be resected during repeat dacryocystorhinostomy.

In Welham and Wulc's[1] study of 208 dacryocystorhinostomy failures, problems with the bony ostium were found in over half the cases and represented the most common cause of dacryocystorhinostomy failure. For external dacryocystorhinostomy, most authors recommend a relatively large osteotomy that eliminates all bone between the lacrimal sac and nasal mucosa,[1,11] that ensures that no bone is left within 5 mm of the common canaliculus,[1] and that measures at least 15 mm in diameter.[2,12-14] Two recent studies of transnasal laser dacryocystorhinostomy have recommended a smaller bony ostium measuring 5 to 7 mm.[15,16] This recommendation may not be applicable to external dacryocystorhinostomy. In our study, the previous ostium was improperly located in three patients (Cases 2, 3, and 5), and did not meet the usually recommended size criteria in one patient (Case 1). Bone regrowth after dacryocystorhinostomy is unusual,[1,2] is more common in children,[1] and apparently developed in Case 4 of our study. Computed tomography or computed tomographic dacryocystography facilitated reoperation after dacryocystorhinostomy failure by determining what modifications were required in the bony ostium.

A transnasal endoscopic approach to dacryocystorhinostomy failure has been described in two recent studies.[4,7] This approach has the advantage of avoiding a skin incision. It also allows examination and correction of intranasal abnormalities. Orcutt, Hillel, and Weymuller[7] stated that a preoperative assessment of bony ostium by use of conventional dacryocystography or computed tomography was a prerequisite for this approach. In every case in our study, computed tomography or computed tomographic dacryocystography detected a problem with the bony ostium and an external dacryocystorhinostomy was performed through a skin incision. If preoperative imaging studies indicate that the bony ostium is of adequate size and location, a transnasal endoscopic approach can be considered.

Anatomic variations and diseases of the nasal cavity and sinuses are other important causes of dacryocystorhinostomy failure,[1,3,4,6,7] and factored in two of our cases. Examination with a nasal speculum or endoscope, or both, can often detect these problems.[4] Computed tomography or computed tomographic dacryocystography may also provide additional information in some cases.

Other reports on the use of computed tomography in the evaluation of dacryocystorhinostomy failure have appeared in the literature. Computed tomography has documented dacryocystorhinostomy failure from tumors,[3,5,6] orbital pseudotumor,[3] and nasal septal deviation.[7] Computed tomography has demonstrated that persistent epiphora after dacryocystorhinostomy was a result of a basilar skull fracture causing a cerebrospinal fluid leak.[8] Computed tomography has been used to evaluate the adequacy of the bony ostium before endoscopic repair of dacryocystorhinostomy failure.[7]

In our method of computed tomographic dacryocystography, a radiopaque agent was injected into the lacrimal sac through a catheter placed in the lower canaliculus. Zinreich and associates[9] devised a method of computed tomographic dacryocystography in which metrizamide eyedrops were placed into the conjunctival cul-de-sac. By obviating the need for canalicular intubation, their method increases patient comfort, can be performed in children, and eliminates the need for a physician or technician skilled in canalicular intubation. Although we suspect that our method might result in better filling of the lacrimal sac in some cases, we do not have any experience with their method.

In the computed tomographic dacryocystograms in our study, there was a delay of approximately 15 minutes between the instillation of radiopaque agent and the performance of the computed tomography. This delay was caused by our early inefficiency in coordinating the two steps. We have subsequently eliminated these inefficiencies and now perform the computed tomography immediately after the instillation of the dye.

As conventional dacryocystography and computed tomography are already performed in many institutions, computed tomographic dacryocystography can easily be implemented with only minor adaptation of preexisting techniques. This technique can be performed on most repeat dacryocystorhinostomy candidates, but obviously cannot be performed on patients who have total canalicular obstructions. After previous dacryocystorhinostomy failure, identification of the lacrimal sac on computed tomography and during surgery may be challenging because of scarring and alteration of anatomic landmarks. By identifying the lacrimal sac's shape, location, and relation to surrounding structures, computed tomographic dacryocystography facilitates the treatment of these difficult cases.

References

1. Welham, R. A. N., and Wulc, A. E.: Management of unsuccessful lacrimal surgery. Br. J. Ophthalmol. 71:152, 1987.
2. McLachlan, D. L., Shannon, G. M., and Flanagan, J. C.: Results of dacryocystorhinostomy. Analysis of the reoperations. Ophthalmic Surg. 11:427, 1980.
3. Hurwitz, J. J., and Victor, W. H.: The role of sophisticated radiological testing in the assessment and management of epiphora. Ophthalmology 92:407, 1985.
4. Allen, K. M., Berlin, A. J., and Levine, H. L.: Intranasal endoscopic analysis of dacryocystorhinostomy failure. Ophthalmic Plast. Reconstr. Surg. 4:143, 1988.
5. Carnevali, L., Trimarchi, F., Rosso, R., and Stringa, M.: Haemangiopericytoma of the lacrimal sac. A case report. Br. J. Ophthalmol. 72:782, 1988.
6. Sternberg, I., and Levine, M. R.: Ethmoidal sinus osteoma. A primary cause of nasolacrimal duct obstruction and dacryocystorhinostomy failure. Ophthalmic Surg. 15:295, 1984.
7. Orcutt, J. C., Hillel, A., and Weymuller, E. A.: Endoscopic repair of failed dacryocystorhinostomy. Ophthalmic Plast. Reconstr. Surg. 6:197, 1990.
8. Dryden, R. M., and Wulc, A. E.: Pseudo-

epiphora from cerebrospinal fluid leak. Case report. Br. J. Ophthalmol. 70:570, 1986.

9. Zinreich, S. J., Miller, N. R., Freeman, L. N., Glorioso, L. W., and Rosenbaum, A. E.: Computed tomographic dacryocystography using topical contrast media for lacrimal system visualization. Orbit 9:79, 1990.

10. Serdahl, C. L., Berris, C. E., and Chole, R. A.: Nasolacrimal duct obstruction after endoscopic sinus surgery. Arch. Ophthalmol. 108:391, 1990.

11. Putterman, A. M.: Oculoplastic surgery. In Peyman, G. A., Sanders, D. R., and Goldberg, M. F. (eds.): Principles and Practice of Ophthalmology. Philadelphia, W. B. Saunders Co., 1980, pp. 2281–2288.

12. McPherson, S. D., and Egleston, D.: Dacryocystorhinostomy. A review of 106 operations. Am. J. Ophthalmol. 47:328, 1959.

13. Hecht, S. D.: Dacryocystorhinostomy. In Hornblass, A., and Hanig, C. J. (eds.): Oculoplastic, Orbital, and Reconstructive Surgery. Baltimore, Williams & Wilkins, 1990, pp. 1433–1440.

14. Patrinely, J. R., and Anderson, R. L.: A review of lacrimal drainage surgery. Ophthalmic Plast. Reconstr. Surg. 2:97, 1986.

15. Massaro, B. M., Gonnering, R. S., and Harris, G. J.: Endonasal laser dacryocystorhinostomy. A new approach to nasolacrimal duct obstruction. Arch. Ophthalmol. 108:1172, 1990.

16. Gonnering, R. S., Lyon, D. B., and Fisher, J. C.: Endoscopic laser-assisted lacrimal surgery. Am. J. Ophthalmol. 111:152, 1991.

OPHTHALMIC MINIATURE

And as I faced him, with levelled gun shaking in my hands, I had time to note the worn and haggard appearance of his face. It was as if some strong anxiety had wasted it. The cheeks were sunken, and there was a wearied, puckered expression on the brow. And it seemed to me that his eyes were strange, not only the expression, but the physical seeming, as though the optic nerves and supporting muscles had suffered strain and slightly twisted the eyeballs.

Jack London, *The Sea Wolf*
New York, Bantam Books, 1986, p. 208

Congenital Entropion With Intact Lower Eyelid Retractor Insertion

George B. Bartley, M.D., Jeffrey A. Nerad, M.D., Robert C. Kersten, M.D.,
and Leo J. Maguire, M.D.

Congenital lower eyelid entropion is generally considered to result from improper development of the retractor aponeurosis insertion to the inferior portion of the tarsal plate. We treated three patients with this uncommon disorder. At operation, aponeurotic defects were anticipated and specifically sought, but in each case the lower eyelid retractors were inserted normally. In two patients, entropion was relieved by surgical disinsertion and then advancement of the retractors. In the third patient, who also had multiple concomitant facial and systemic developmental anomalies, improvement in the lower eyelid malpositions required a combination of procedures. The intraoperative findings in our patients demonstrate that disinsertion of the lower eyelid retractors is not a universal etiologic mechanism in congenital entropion.

TRUE CONGENITAL lower eyelid entropion is uncommon; at one eye clinic only a single case was observed among 160,000 patients over a 25-year period.[1] Epiblepharon, in contrast, is common, especially in Japanese children, 24% of whom have the condition at the age of 1 year.[2] Differentiation between the two disorders is important. Marked corneal irritation is infrequent with epiblepharon, which typically resolves spontaneously as the child's face develops. Congenital entropion, however, often requires prompt surgical intervention to prevent potentially blinding corneal scarring.

The putative etiologic mechanism for congenital lower eyelid entropion is improper development of the retractor aponeurosis insertion.[3,4] We treated three patients with this uncommon eyelid malposition. At operation, aponeurotic defects were anticipated and specifically sought, but in each case the lower eyelid retractors were inserted normally.

Case Reports

Case 1

A male infant was born after a normal 40-week gestation; the vaginal delivery was uncomplicated. Matter from both eyes was observed on the first postpartum day, and erythro-

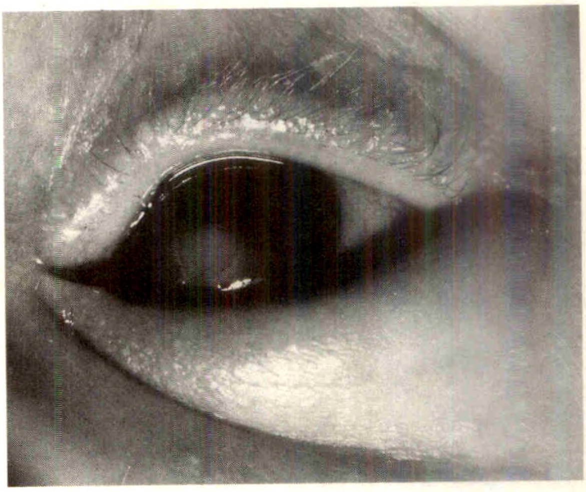

Fig. 1 (Bartley and associates). Case 1. Congenital entropion of left lower eyelid with a secondary corneal ulcer in a 3-week-old male infant.

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From the Department of Ophthalmology (Drs. Bartley and Maguire), Mayo Clinic and Mayo Foundation, Rochester, Minnesota; Department of Ophthalmology, University of Iowa, Iowa City, Iowa (Dr. Nerad); and Department of Ophthalmology, University of Cincinnati Hospital, Cincinnati, Ohio (Dr. Kersten). This study was supported by an unrestricted grant from Research to Prevent Blindness, Inc.

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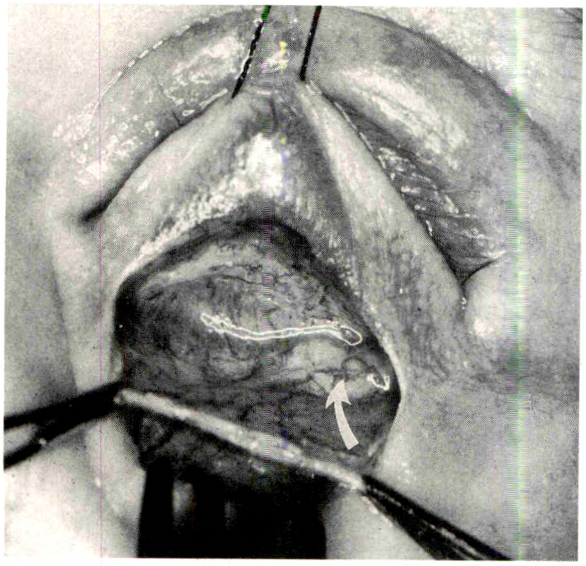

Fig. 2 (Bartley and associates). Case 1. The orbital septum (held by forceps) has been dissected from the underlying capsulopalpebral fascia. The lower eyelid retractors were intact. The arrow identifies preaponeurotic fat.

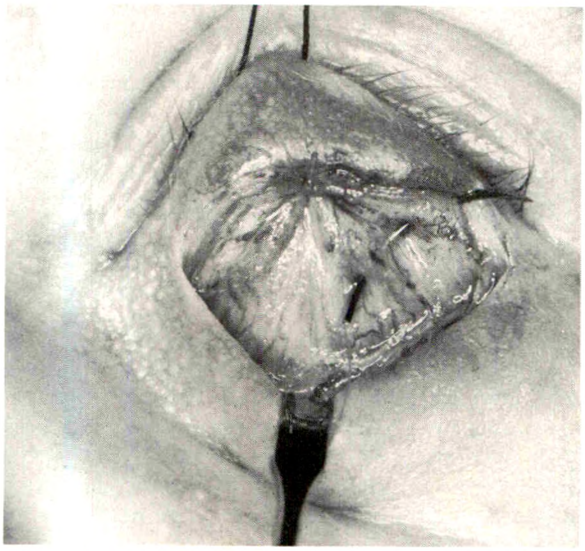

Fig. 3 (Bartley and associates). Case 1. The lower eyelid retractors were surgically disinserted, resected, and reattached to the inferior tarsal edge.

mycin ointment was prescribed by a pediatrician. Inflammation of the right eye quickly resolved, but discharge from the left eye persisted. A white opacity was apparent on the left cornea at 2 weeks of age, and the child was referred to an ophthalmologist. A corneal ulcer was diagnosed, scrapings were taken for culture (which ultimately were negative), and hourly administration of tobramycin drops and polymyxin B–bacitracin ointment was prescribed.

The patient was subsequently examined at 3 weeks of age by one of us (L.J.M.), who confirmed the diagnosis of a corneal ulcer and observed that the left lower eyelid was rotated inward against the globe. Later that same day, the eyelid was operated on by one of us (G.B.B.), and the cornea was examined and cultured (Fig. 1). The skin was incised in a faint eyelid crease near the inferior edge of the tarsus. The orbicularis was divided horizontally,

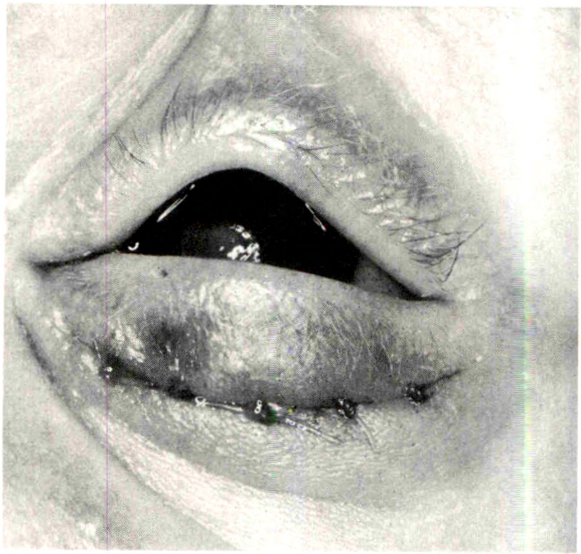

Fig. 4 (Bartley and associates). Case 1. A minimal ectropion of the eyelid margin was desired to facilitate healing of the corneal ulcer.

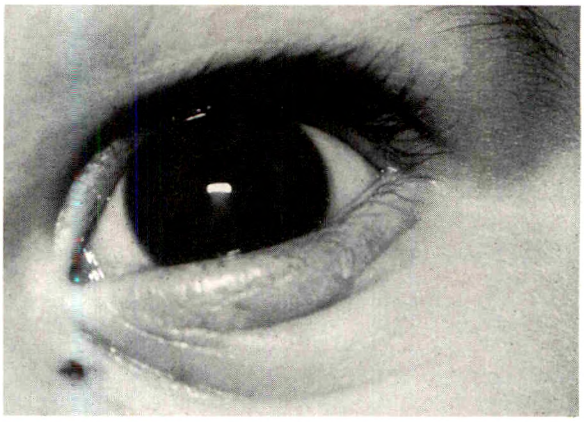

Fig. 5 (Bartley and associates). Case 1. Residual corneal scar and satisfactory eyelid position four months after surgery.

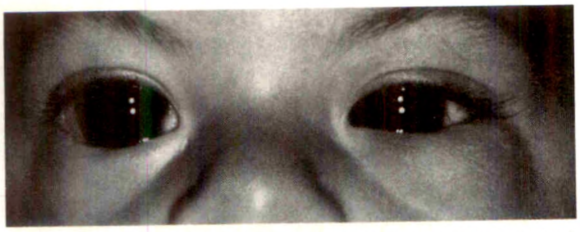

Fig. 6 (Bartley and associates). Case 2. Congenital bilateral lower eyelid entropion in a 13-month-old girl.

and the orbital septum was dissected from the lower eyelid retractors. An aponeurotic disinsertion was sought, but the insertion of the retractors appeared normal (Fig. 2). Plication of the retractors to the inferior edge of the tarsus with a silk suture caused the eyelid to rotate moderately away from the globe, so the suture was removed. The retractors were surgically disinserted and a small distal portion was resected. The aponeurosis was reattached to the inferior tarsal border with three interrupted 5-0 chromic sutures (Fig. 3). A minimal overcorrection (slight eversion) of the eyelid margin (Fig. 4) was desired to ensure that the cornea would not be abraded, and the ultimate eyelid position was hoped to be normal once the chromic sutures absorbed.

After surgery, fortified gentamicin and vancomycin eyedrops were prescribed, and the corneal ulcer healed rapidly. A small corneal scar persisted, but it was inferior to the visual axis. The lower eyelid was in normal position four months after surgery (Fig. 5), and no complications developed during a follow-up of ten months.

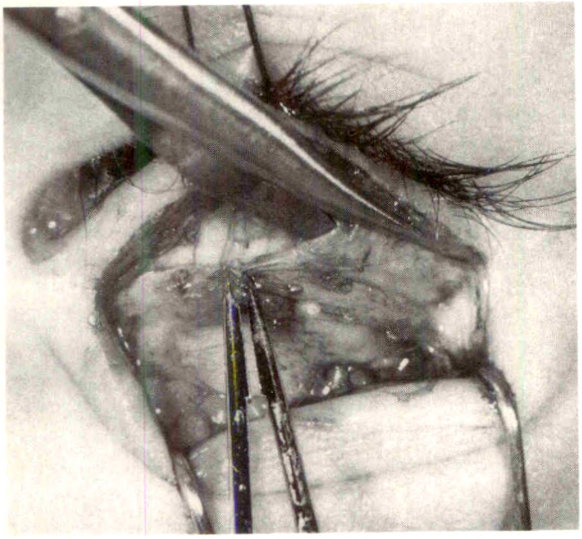

Fig. 8 (Bartley and associates). Case 2. The lower eyelid retractors were surgically disinserted, resected, and reattached to the inferior tarsal edge.

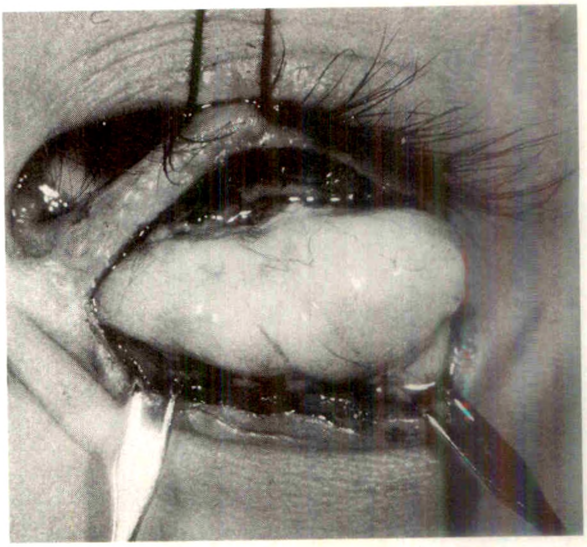

Fig. 7 (Bartley and associates). Case 2. Abnormally abundant fat that was excised. The lower eyelid retractors were intact.

Case 2

Bilateral lower eyelid entropion was observed by one of us (J.A.N.) in a 10-week-old female infant with a 6-p and 13-q balance translocation. In addition to the eyelid malpositions, the child had congenital glaucoma, nasolacrimal drainage abnormalities, persistent hyaloid vessels, cleft palate, club feet, and lacked a corpus callosum. The corneas tolerated the entropion satisfactorily until the age of 13 months (Fig. 6),

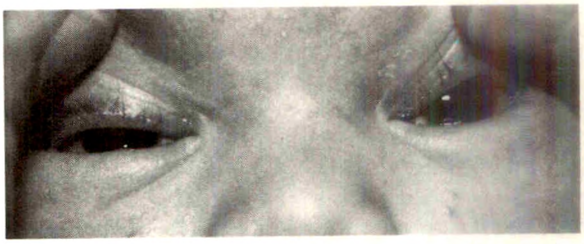

Fig. 9 (Bartley and associates). Case 3. Congenital bilateral lower eyelid entropion in a 2-week-old male infant. The lower eyelid retractors were intact.

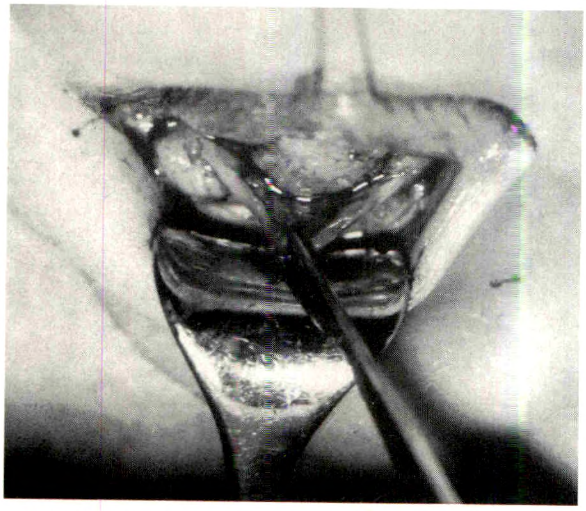

Fig. 10 (Bartley and associates). Case 3. The lower eyelid retractors (held by forceps) were surgically disinserted, resected, and reattached to the inferior tarsal edge.

when operation was required. The lower eyelid retractors were carefully inspected and were intact, but there was a greater than normal amount of fat in the eyelids (Fig. 7), possibly caused by a defect in the orbital septum. The fat was excised, and the retractors were surgically disinserted (Fig. 8), resected slightly, and reattached to the inferior tarsal edge. The entropion was improved, but persistent corneal irritation necessitated two additional operations (another bilateral retractor advancement and tarsal strip procedure on the left lower eyelid; canthoplasty on the right lower eyelid and tarsotomy and marginal rotation on the left lower eyelid) to achieve a satisfactory eyelid position. Although the right lower eyelid was slightly rotated inward against the globe at the most recent examination (two years after surgery), the corneas were clear without staining.

Case 3

A 2-week-old male infant with a history of bilateral conjunctivitis since birth was found by one of us (R.C.K.) to have true entropion of both lower eyelids (Fig. 9). The inferior corneal epithelium of each eye stained with fluorescein, but there was no ulceration. The lower eyelids were operated on through a subciliary incision; the retractor aponeurosis was bilaterally intact. The retractors were surgically disinserted, resected 3 to 4 mm, and secured to the inferior tarsal border (Fig. 10). Additionally, a small strip of preseptal orbicularis muscle was excised. The entropion was relieved (Fig. 11), and no complications had developed during a follow-up of one year.

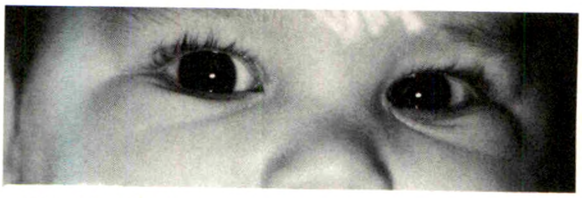

Fig. 11 (Bartley and associates). Case 3. Normal eyelid positions three months after surgery.

Discussion

The etiologic mechanisms for upper and lower eyelid entropion are distinct. Inversion of the upper eyelid usually is associated with an inchoate or deformed tarsal plate; in its extreme form, this anomaly is referred to as the tarsal kink syndrome.[5-11] Of the various theories that have been proposed to explain the cause of congenital lower eyelid entropion, only two have been favored.

In 1907, Léblond[12] attributed inversion of the eyelid to hypertrophy and overaction of the marginal orbicularis fibers, a view that was reasserted by von Herrenschwand[13,14] in 1916 and 1917 and by Fox[15] in his 1956 review of the topic. Leblond's etiologic mechanism was generally accepted until 1983, when Tse, Anderson, and Fratkin[3] demonstrated histologically that the orbicularis fibers near the eyelid margin were not hypertrophied. The authors postulated from their findings in three patients that disinsertion of the retractor aponeurosis from its normal attachments to the inferior portion of the tarsal plate is the most likely origin of congenital lower eyelid entropion. A similar mechanism was hypothesized by Quickert, Wilkes, and Dryden[4] in an independent report two months later, and since then it has been considered the primary cause of this uncommon congenital eyelid malposition.

The intraoperative findings in our three patients demonstrated that disinsertion of the lower eyelid retractors is not a universal etiologic mechanism in true congenital entropion. No new anatomic reason for the eyelid malpositions was apparent, however, by either clinical examination or surgical exploration. In Case 2, the abnormally abundant orbital fat within the anterior portion of the eyelid may have exerted a mechanical effect on the eyelid margin. Cases

1 and 3 exhibited spasm of the pretarsal orbicularis in that the eyelid margins could be everted to a normal position, but they would immediately rotate inward against the globe with a blink. We agree with Tse, Anderson, and Fratkin[3] that overaction or apparent hypertrophy of the pretarsal orbicularis may be secondary to ocular irritation and is not the underlying mechanism for the entropion.

The successful surgical results achieved in Cases 1 and 3 by resecting and advancing the aponeurosis might be interpreted as tacit evidence for a retractor defect. A similar operation is commonly used for involutional entropion, however, even though disinsertion of the lower eyelid retractors is not always clinically apparent and has not been demonstrated histopathologically.[16]

The anatomic relationship of the lower eyelid retractors to the tarsal plate in congenital entropion would best be studied with cross sections of a full-thickness wedge resection, as was done by Hawes and Dortzbach[16] in their study of adults. Such specimens, unfortunately, are usually not obtained as an incidental consequence of congenital entropion repair because horizontal laxity is not typical. We hope that this study will stimulate others to obtain tissue for histopathologic analysis in patients with this uncommon disorder, if clinically appropriate.

ACKNOWLEDGMENT

Niloofar Z. Gharagozloo, M.D., translated reference 12 and Helmut Buettner, M.D., translated references 13 and 14.

References

1. Czukrasz, I.: Congenital entropion due to epiblepharon. Br. J. Ophthalmol. 34:318, 1950.

2. Noda, S., Hayasaka, S., and Setogawa, T.: Epiblepharon with inverted eyelashes in Japanese children. I. Incidence and symptoms. Br. J. Ophthalmol. 73:126, 1989.

3. Tse, D. T., Anderson, R. L., and Fratkin, J. D.: Aponeurosis disinsertion in congenital entropion. Arch. Ophthalmol. 101:436, 1983.

4. Quickert, M. H., Wilkes, T. D. I., and Dryden, R. M.: Nonincisional correction of epiblepharon and congenital entropion. Arch. Ophthalmol. 101:778, 1983.

5. Callahan, A.: Reconstructive Surgery of the Eyelids and Ocular Adnexa. Birmingham, Alabama, Aesculapius Publishing Company, 1966, pp. 37–40.

6. Hiles, D. A., and Wilder, L. W.: Congenital entropion of the upper lids. J. Pediatr. Ophthalmol. 6:157, 1969.

7. Biglan, A. W., and Buerger, G. F.: Congenital horizontal tarsal kink. Am. J. Ophthalmol. 89:522, 1980.

8. Zak, T. A.: Congenital primary upper eyelid entropion. J. Pediatr. Ophthalmol. Strabismus 21:69, 1984.

9. McCarthy, R. W.: Lamellar tarsoplasty. A new technique for correction of horizontal tarsal kink. Ophthalmic Surg. 15:859, 1984.

10. Bosniak, S., Hornblass, A., and Smith, B.: Reexamining the tarsal kink syndrome. Considerations of its etiology and treatment. Ophthalmic Surg. 16:437, 1985.

11. Price, N. C., and Collin, J. R. O.: Congenital horizontal tarsal kink. A simple surgical correction. Br. J. Ophthalmol. 71:204, 1987.

12. Léblond, É.: Étiologie de l'entropion congénital. Arch. Ophtalmol. 27:782, 1907.

13. von Herrenschwand, F.: Entropium palpebrarum congenitum. Klin. Monatsbl. Augenheilkd. 56:509, 1916.

14. von Herrenschwand, F.: Ueber Entropium congenitum und Epiblepharon. Klin. Monatsbl. Augenheilkd. 58:385, 1917.

15. Fox, S. A.: Primary congenital entropion. Arch. Ophthalmol. 56:839, 1956.

16. Hawes, M. J., and Dortzbach, R. K.: The microscopic anatomy of the lower eyelid retractors. Arch. Ophthalmol. 100:1313, 1982.

Retinoblastoma Manifesting as Orbital Cellulitis

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Robert P. Schroeder, M.D., and Patrick DePotter, M.D.

Five children with previously undiagnosed retinoblastoma had signs of unilateral orbital cellulitis and were treated with systemic antibiotics, corticosteroids, or both. When retinoblastoma was finally diagnosed clinically, radiologists believed in every case that, on the basis of the soft-tissue swelling seen with computed tomography, there was orbital extension of the tumor. However, intraoperative and histopathologic observations disclosed no demonstrable orbital tumor involvement. The affected eyes all had neovascular glaucoma, and all harbored highly necrotic tumors that were contained within the eye. We concluded that orbital inflammation can occur with retinoblastoma confined to the eye and that signs of orbital cellulitis do not necessarily imply orbital extension of the tumor.

LEUKOCORIA AND STRABISMUS are the most common clinical manifestations of retinoblastoma.[1-3] More unusual manifestations include pseudohypopyon, neovascular glaucoma, and spontaneous hyphema.[1,3-8] In rare instances retinoblastoma can produce clinical findings suggestive of panophthalmitis or orbital cellulitis.[1,9-14] We treated five children with bilateral sporadic retinoblastoma who initially had clinical and radiographic signs of orbital cellulitis in one eye and who were initially treated with corticosteroids, antibiotics, or both. When the diagnosis of retinoblastoma was subsequently made, ophthalmologists and radiologists believed that the anterior orbital and adnexal signs indicated orbital extension of the tumor. However, in every case the inflammatory signs were actually secondary to a necrotic retinoblastoma that was still contained within the eye. Awareness of this unusual manifestation of retinoblastoma can prevent delayed diagnosis and misdirected therapy.

Patients and Methods

The computerized diagnostic files of all patients with retinoblastoma on file in the Oncology Service at our institution were reviewed. The charts of all children with preseptal or orbital cellulitis as part of the initial manifestation were studied in greater detail. The patients' clinical history, clinical findings, computed tomograms, and pathologic observations served as the basis of this report.

From February 1974 through February 1991, 450 new patients with retinoblastoma were examined by the Oncology Service. Of these, six patients (1.3%) had signs of orbital cellulitis as the initial clinical manifestation of retinoblastoma. One case was excluded because the child was treated elsewhere. The following case histories summarize findings in these five cases.

Case Reports

Case 1

In 1980, a previously healthy 4-month-old boy developed rapid onset of redness and edema of the left upper eyelid (Fig. 1, top left). The diagnosis of preseptal cellulitis was made, cultures of the eyelid margins disclosed *Staphylococcus aureus*, and systemic antibiotics were initiated. An orbital computed tomogram showed a large calcified mass filling most of the enlarged left globe with marked, periocular soft-tissue swelling, suggesting extrascleral extension of retinoblastoma (Fig. 1, top right).

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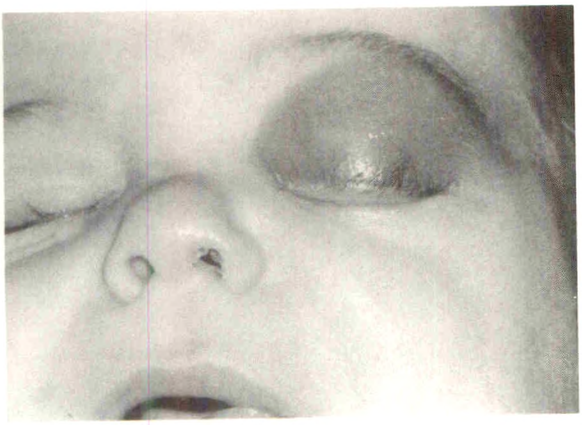
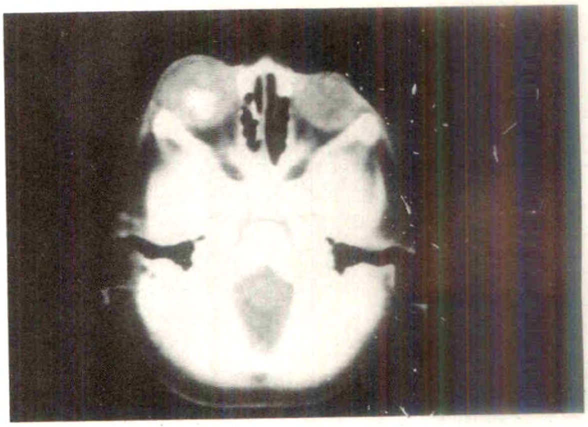
Reprint requests to Jerry A. Shields, M.D., Director, Ocular Oncology Service, Wills Eye Hospital, Ninth and Walnut Sts., Philadelphia, PA 19107.

The patient was referred to us for diagnosis and treatment.

Our examination disclosed a total retinal detachment secondary to advanced retinoblastoma in the left eye and six smaller retinoblastomas in the right eye. The tumors in both eyes were confirmed by ultrasonography. The left eye had an intraocular pressure of 50 mm Hg and iris neovascularization, and it was enucleated. No evidence of extraocular tumor extension was seen at surgery. Histopathologic findings disclosed a poorly differentiated, necrotic retinoblastoma and iris neovascularization. There was no gross (Fig. 1, bottom left) or microscopic evidence of extraocular extension of retinoblastoma. The final diagnosis was bilateral sporadic retinoblastoma with neovascular glaucoma and orbital cellulitis secondary to necrotic retinoblastoma in the left eye. The right eye was successfully treated with external





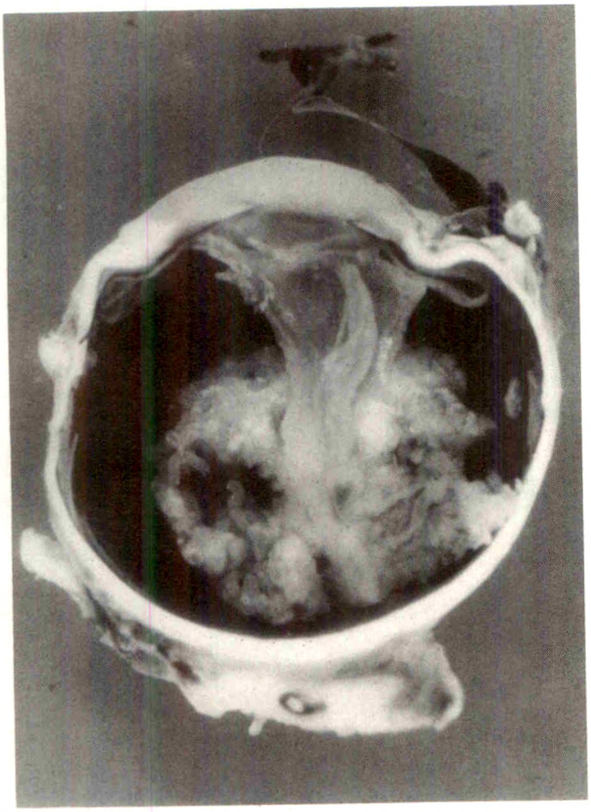


Fig. 1 (Shields and associates). Case 1. Top left, Clinical appearance showing redness and edema of left upper eyelid. Top right, Orbital computed tomogram showing large left globe filled with a calcified tumor and soft-tissue swelling anteriorly. Bottom left, Sectioned eye showing necrotic exophytic retinoblastoma.

beam radiotherapy. Ten years later the child was alive and well with visual acuity of 20/40 in the right eye.

Case 2

In 1986, a 14-month-old girl developed rapid onset of edema of the left upper eyelid (Fig. 2, top left) and conjunctival chemosis (Fig. 2, top right) over a 24-hour period. Orbital cellulitis was diagnosed and antibiotics were administered intravenously. An orbital computed tomogram disclosed bilateral intraocular calcified tumors suggestive of retinoblastoma with orbital extension of the tumor in the left eye (Fig. 2, bottom left). The patient was promptly referred to us.

The fundus of the right eye disclosed a solitary retinoblastoma near the equator superonasally measuring 9 × 7 × 4.5 mm. The left eye had an intraocular pressure of 50 mm Hg, extensive edema of the upper eyelid (Fig. 2, top left) and conjunctiva (Fig. 2, top right), corneal edema, iris neovascularization, a small hyphema, and no clear view of the fundus. The tumors in both eyes were confirmed by ultrasonography. The left eye was enucleated and the tumor in the right eye was treated with a radioactive ruthenium plaque.

Gross examination of the sectioned left globe disclosed a necrotic retinoblastoma (Fig. 2, bottom right). Microscopic examination showed a necrotic calcified tumor with iris neovascularization and secondary angle closure. There was no gross or microscopic evidence of choroidal,

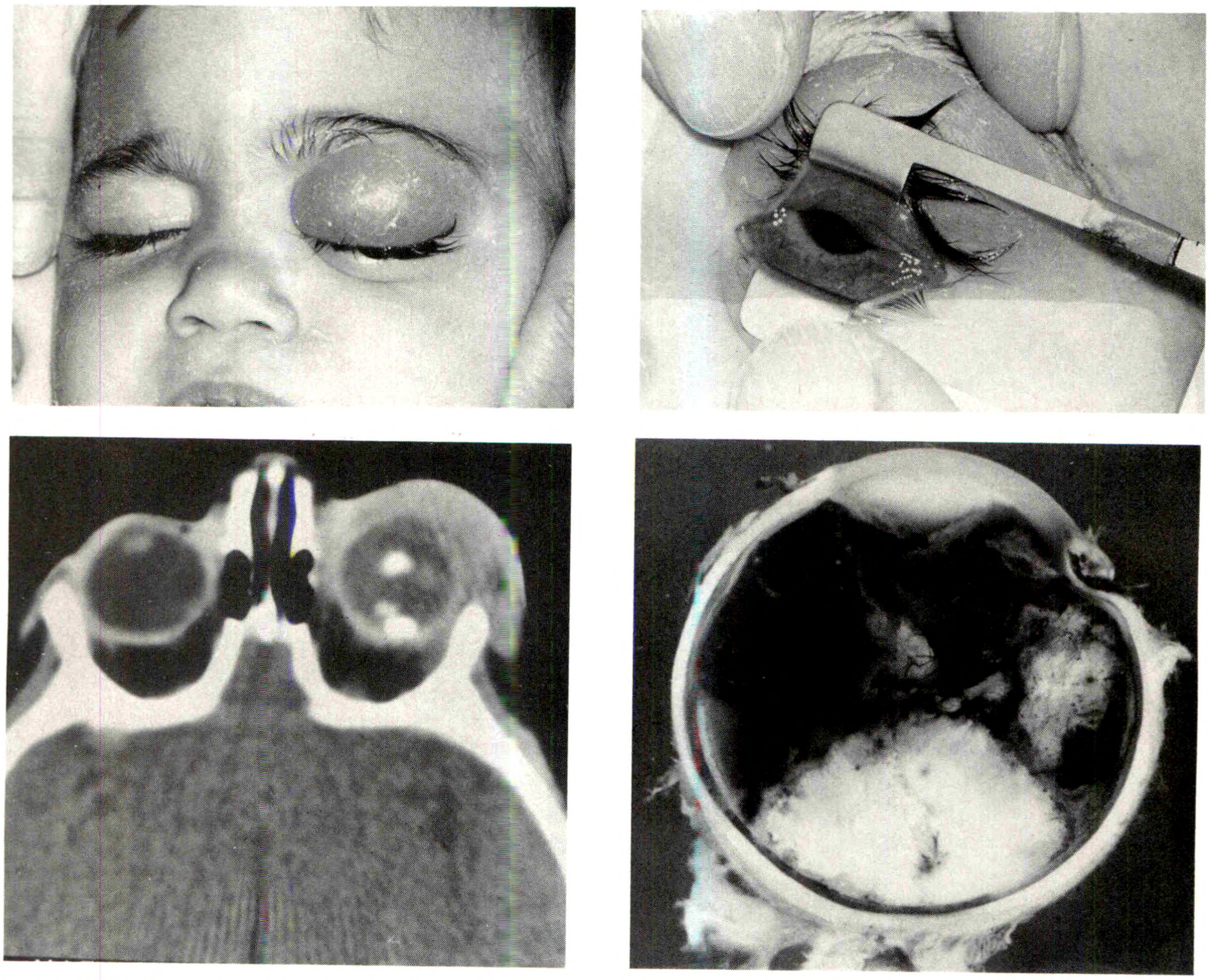


Fig. 2 (Shields and associates). Case 2. Top left, Clinical appearance showing redness and swelling of left upper eyelid. Top right, Clinical appearance of conjunctival chemosis. Bottom left, Orbital computed tomogram showing calcified intraocular mass and soft-tissue swelling anteriorly. Bottom right, Sectioned globe showing calcified retinoblastoma.

optic nerve, or extraocular extension of the tumor. The final diagnosis was bilateral sporadic retinoblastoma with neovascular glaucoma and preseptal cellulitis secondary to necrotic retinoblastoma in the left eye. The patient is alive and well with visual acuity in the right eye of 20/30 almost five years after initial manifestation.

Case 3

A 4-month-old boy developed fever and rapid onset of redness and swelling of the left upper eyelid. He was hospitalized and treated with systemic antibiotics for several days for presumed orbital cellulitis. The patient was referred to us because of a possible left orbital tumor. The left upper eyelid was erythematous and edematous (Fig. 3, top left). Corneal edema and blood and tumor cells in the anterior chamber obscured a view of the fundus. The fundus of the right eye disclosed a large, peripapillary, exophytic retinoblastoma measuring 15 × 14 × 8.0 mm with multiple subretinal seeds and a total retinal detachment. Calcified retinoblastomas were confirmed in both eyes by ultrasonography. The intraocular pressures were R.E.: 13 mm Hg and L.E.: 60 mm Hg.

An orbital computed tomogram demonstrated bilateral calcified intraocular tumors. There was anterior orbital soft-tissue swelling on the left side, suggestive of extraocular extension of retinoblastoma (Fig. 3, top right). The left eye was enucleated, and the right eye was treated with external beam radiotherapy.

Gross examination of the sectioned left eye disclosed a large necrotic retinoblastoma that filled most of the globe (Fig. 3, bottom left). Microscopic examination showed a poorly differentiated necrotic retinoblastoma with extensive iris neovascularization and angle closure. There was no extrascleral extension or optic nerve involvement. The large macular tumor in

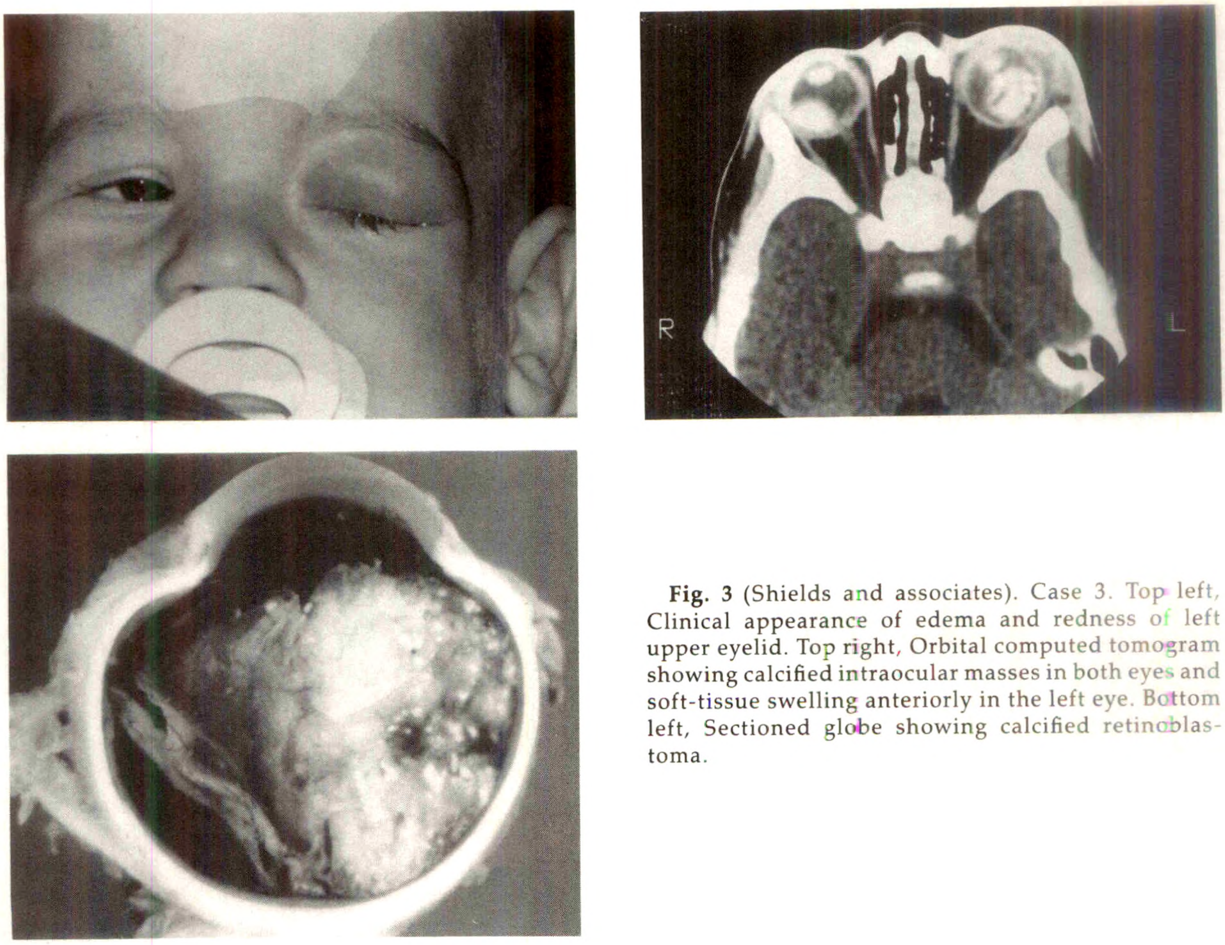


Fig. 3 (Shields and associates). Case 3. Top left, Clinical appearance of edema and redness of left upper eyelid. Top right, Orbital computed tomogram showing calcified intraocular masses in both eyes and soft-tissue swelling anteriorly in the left eye. Bottom left, Sectioned globe showing calcified retinoblastoma.

the right eye responded well to radiotherapy, and 4½ years after initial manifestation, visual acuity was counting fingers.

Case 4

In 1989, a previously healthy 2-month-old boy was observed by the parents to have progressive redness and swelling of the left upper eyelid. The child was referred to the Oncology Service. Examination of the right eye showed a large bilobed retinoblastoma measuring 18 × 16 × 9 mm. It occupied all of the posterior fundus and overhung the optic nerve on the temporal side.

Examination of the left eye showed marked erythema and edema of the upper eyelid (Fig. 4, top left), conjunctival chemosis (Fig. 4, top right), corneal edema, iris neovascularization, intraocular pressure of 30 mm Hg, and almost total replacement of the intraocular contents by a large retinoblastoma. Ultrasonography confirmed the presence of bilateral retinoblastoma. An orbital computed tomogram showed advanced calcified retinoblastoma in both eyes with extensive soft-tissue swelling in the anterior aspect of the left orbit (Fig. 4, bottom left), suggesting orbital extension of the retinoblastoma.

The left eye was enucleated and the right eye was treated with radiotherapy. Gross examination of the sectioned left eye showed a large retinoblastoma filling the vitreous cavity (Fig.

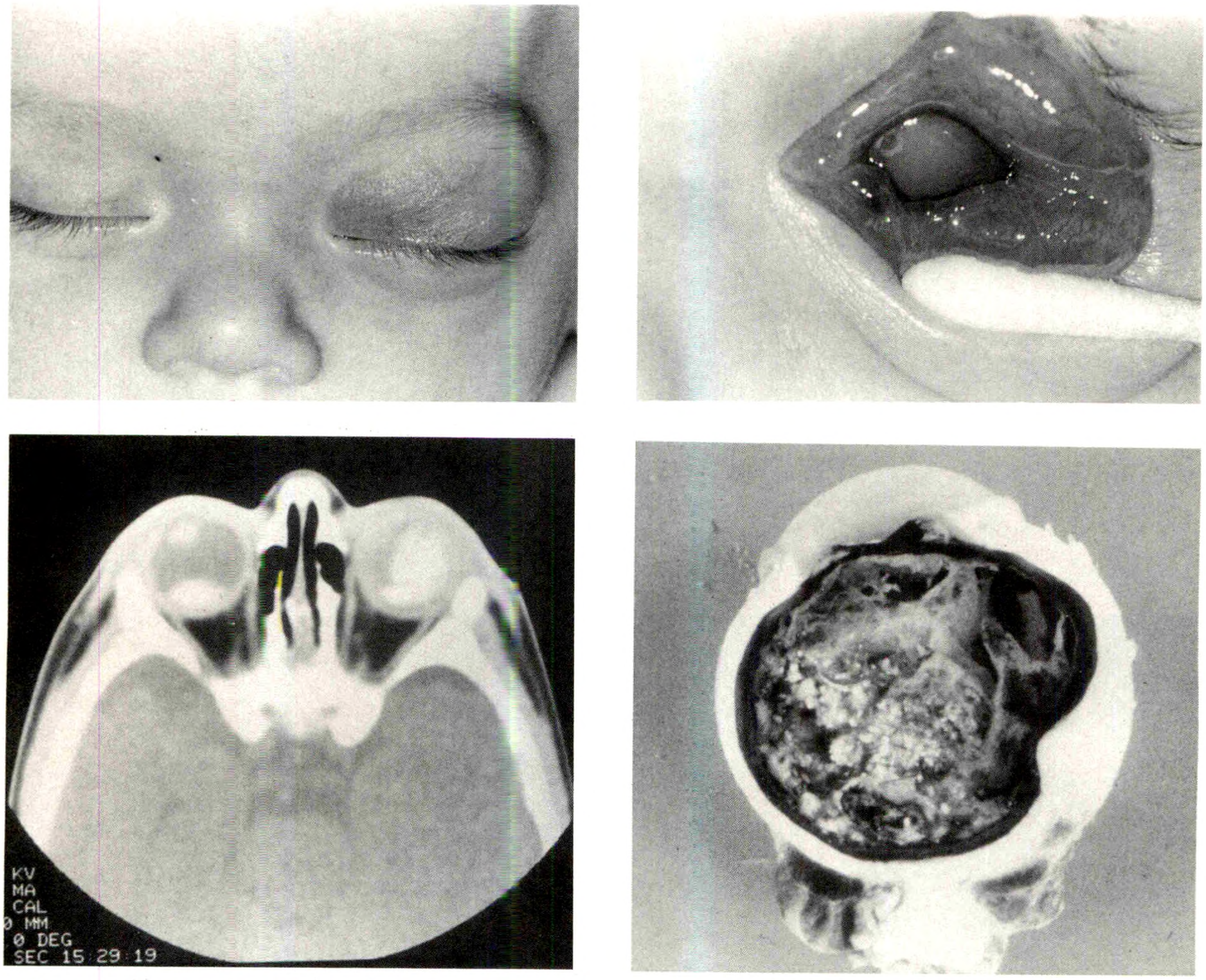


Fig. 4 (Shields and associates). Case 4. Top left, Clinical appearance showing edema and redness of left upper eyelid. Top right, Anterior segment showing marked conjunctival chemosis and corneal edema. Bottom left, Orbital computed tomogram showing bilateral intraocular calcified tumors and soft-tissue swelling of left eye. Bottom right, Sectioned globe showing calcified retinoblastoma.

4, bottom right). Microscopic examination disclosed a fairly well-differentiated but mostly necrotic retinoblastoma with extension into the optic disk to the lamina cribrosa but no evidence of extraocular tumor extension. Extensive neovascularization of the iris was present, and numerous polymorphonuclear leukocytes infiltrated the ciliary body.

Although the large tumor in the right eye showed marked regression and calcification, the patient developed vitreous hemorrhage one year after radiotherapy and has no useful vision.

Case 5

In January 1991, a 2-month-old girl developed sudden redness and edema of the right eyelids (Fig. 5, top left). Examination in an emergency room disclosed slight hyperpyrexia and leukocytosis with a white blood cell count of 14,000 and a normal differential count. The initial diagnosis was orbital cellulitis, and systemic antibiotics were initiated. An orbital computed tomogram disclosed a large calcified mass in the right eye with periocular soft-tissue swelling and a somewhat smaller mass in the left eye. The findings in the right eye were interpreted by radiologists as retinoblastoma with extraocular extension (Fig. 5, top left) and the patient was referred to us.

Our examination disclosed eyelid and conjunctival edema and hyperemia in the right eye with a hazy cornea and iris neovascularization. No view of the fundus was possible in the right

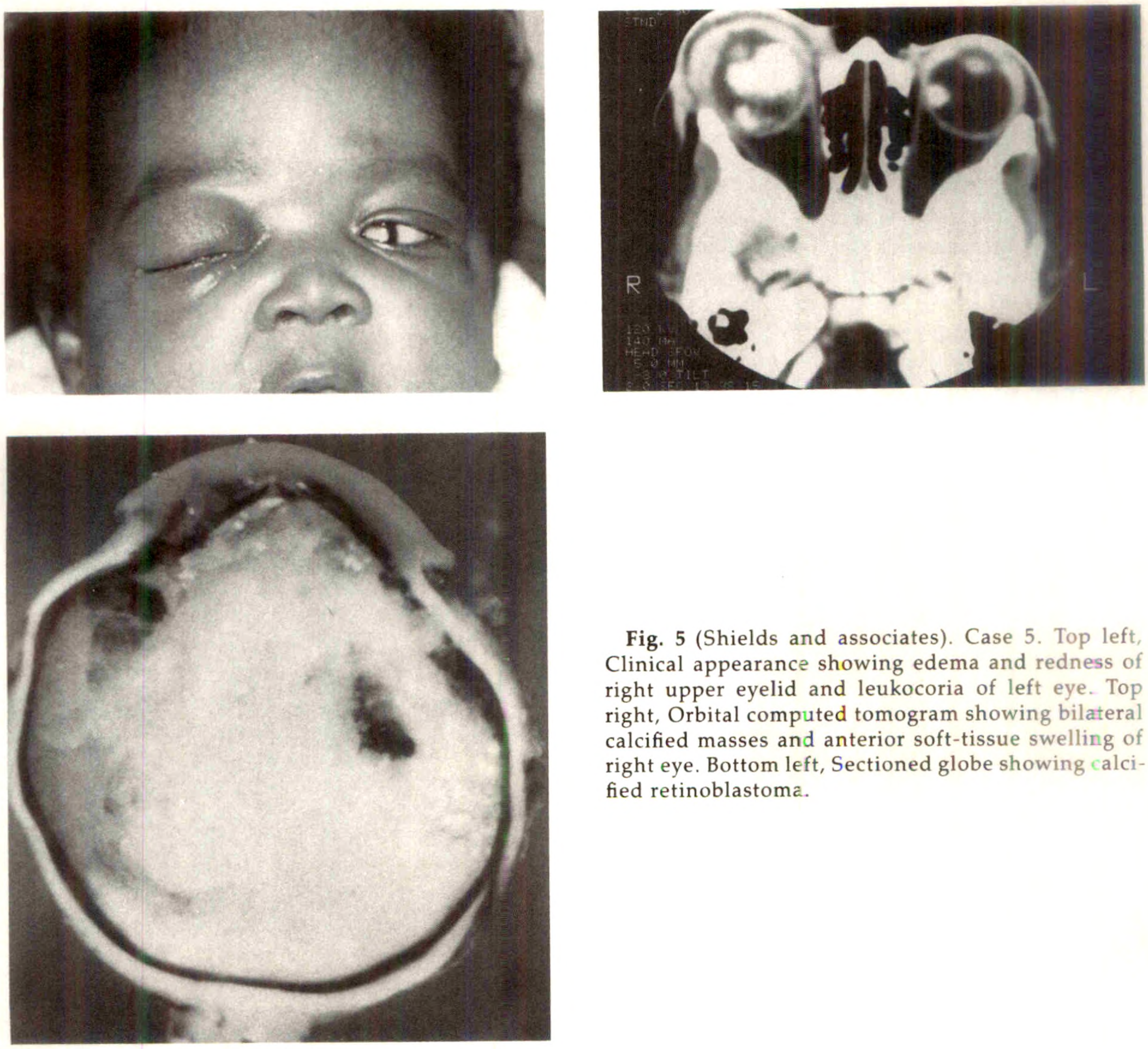


Fig. 5 (Shields and associates). Case 5. Top left, Clinical appearance showing edema and redness of right upper eyelid and leukocoria of left eye. Top right, Orbital computed tomogram showing bilateral calcified masses and anterior soft-tissue swelling of right eye. Bottom left, Sectioned globe showing calcified retinoblastoma.

eye, but a massive nasal retinoblastoma and three smaller temporal tumors were seen in the left eye. The tumors in both eyes were confirmed by ultrasonography.

The right eye was enucleated and the left eye was treated with cryotherapy to the three smaller peripheral tumors and plaque radiotherapy to the larger nasal tumor. The child was doing well six months after treatment.

Gross examination of the sectioned right eye showed a large calcified retinoblastoma (Fig. 5, bottom left). Microscopic examination disclosed a poorly differentiated retinoblastoma with no episcleral extension but there was tumor extension into the anterior portion of the optic nerve. There was iris neovascularization and secondary closure of the anterior chamber angle. Because of the optic nerve involvement, it has been recommended that the child have orbital irradiation and chemotherapy but the parents have not yet agreed to those recommendations.

Discussion

Ocular inflammation is an unusual manifestation of retinoblastoma.[1,9-13] In a review of retinoblastomas on file at the Armed Forces Institute of Pathology, about 7% of cases initially were misdiagnosed as primary ocular inflammation.[9] Only 2% showed the clinical features of panophthalmitis or orbital cellulitis. Such atypical features are often associated with a delay in diagnosis and subsequent higher mortality.[9]

Most cases of retinoblastoma are diagnosed when the tumor is confined to the eye, and orbital extension is an unusual manifestation of retinoblastoma in the United States. Even when orbital extension of retinoblastoma is present, there are usually no major signs of inflammation.[15,16] If orbital extension of retinoblastoma is present, the mortality is higher despite orbital irradiation and chemotherapy.[16] Therefore, it is clinically important to differentiate true orbital cellulitis, inflammation secondary to retinoblastoma, and orbital extension of retinoblastoma.

Children with true orbital cellulitis are more likely to have a history of frontoethmoidal sinusitis, high fever, and severe leukocytosis, and they usually have normal pupils and fundi. An orbital computed tomogram typically shows a normal globe and cloudy sinuses, sometimes with a subperiosteal orbital abscess associated with the orbital inflammatory signs.

In contrast, most children with necrotic retinoblastoma confined within the eye have no high fever or marked leukocytosis (although one of our children had mild fever and one had mild leukocytosis). They generally have leukocoria or an obvious fundus mass. An orbital computed tomogram usually shows the intraocular mass often with calcification and normal sinuses. If computed tomographic evidence of soft-tissue swelling is present, it is usually located in the anterior portion of the orbit or in the optic nerve, and not in the posterior superomedial portion of the orbit adjacent to a cloudy sinus, as seen with true infectious cellulitis. Therefore, the differential diagnosis between retinoblastoma and infectious orbital cellulitis can usually be made easily on the basis of clinical and radiologic findings.

True orbital extension of retinoblastoma has become rare in the United States. Affected patients do not usually have marked eyelid and conjunctival edema as was present in our cases. Proptosis and motility disturbances may be evident, and orbital computed tomograms show a distinct more circumscribed extrascleral mass rather than the diffuse, ill-defined, orbital soft-tissue swelling as seen in our cases.

Fortunately, our five patients all had orbital computed tomography because of suspected orbital cellulitis and this confirmed the presence of retinoblastoma. If the computed tomograms had not been taken, the diagnosis of retinoblastoma could have been delayed. We recommend that all children with signs of preseptal cellulitis have an immediate fundus examination and if the fundus cannot be visualized for any reason, orbital ultrasonography or computed tomography should be performed to exclude the diagnosis of retinoblastoma.

In all of these cases, the radiologists believed that orbital extension of retinoblastoma was present on the basis of computed tomographic findings of soft-tissue swelling adjacent to a calcified intraocular retinoblastoma. In retrospect, careful review of the computed tomograms demonstrated only swelling of the anterior orbital soft tissues and no signs of sinus infection or orbital abscess.

It should be stressed that any child with signs of orbital inflammation should have a detailed ocular examination, including indirect ophthalmoscopy, to visualize the intraocular tumor. If hazy ocular media preclude a view of the fundus, then ultrasonography should be performed to detect a possible retinoblastoma. However, ultrasonography has distinct limitations in the detection of orbital involvement because of the high reflectivity of the intraocular tumor. Consequently, computed tomography or magnetic resonance imaging is necessary in such cases to determine if there is orbital inflammation or extension of retinoblastoma.

Histopathologically, all five enucleated globes with retinoblastoma showed no transscleral extension of the tumor, and only two patients had slight microscopic extension into the optic nerve. The tumors in all five patients were necrotic and had extensive iris neovascularization and secondary angle closure, explaining the severe glaucoma seen clinically. In these patients it is likely that the rapidly growing intraocular tumor became necrotic and induced a secondary regional inflammatory response that led to the clinical signs of orbital cellulitis.

All five of our patients had bilateral retinoblastoma, and one eye developed the inflammatory signs. Although the inflammatory signs could have been secondary to a necrotic tumor that outgrew its blood supply, it is also tempting to speculate that the tumor in one eye could have induced an immunologic reaction that caused necrosis of the tumor in the fellow eye in our five patients.

Because most retinoblastomas that produce such severe inflammatory signs are markedly advanced, the only appropriate management is enucleation.[1-3] In our experience, enucleation in such cases can be very difficult because of the small eye and the tight eyelid swelling. Enucleation in these children should be performed by using a minimal manipulation technique and often a large lateral canthotomy to facilitate removal of the globe after the optic nerve is sectioned.

References

1. Shields, J. A., and Shields, C. L.: Intraocular Tumors. A Text and Atlas, Chap. 18. Philadelphia, W. B. Saunders. In press.
2. Ellsworth, R. M.: The practical management of retinoblastoma. Trans. Am. Ophthalmol. Soc. 67:462, 1969.
3. Shields, J. A., Shields, C. L., Donoso, L. A., and Lieb, W.: Changing concepts in the management of retinoblastoma. Ophthalmic Surg. 21:72, 1990.
4. Binder, P. S.: Unusual manifestations of retinoblastoma. Am. J. Ophthalmol. 77:674, 1974.
5. Shields, J. A., Shields, C. L., Eagle, R. C., Jr., and Blair, C. J.: Spontaneous pseudohypopyon secondary to diffuse infiltrating retinoblastoma. Arch. Ophthalmol. 106:1301, 1988.
6. Shields, C. L., Shields, J. A., and Shields, M. B.: Prevalence and mechanism of secondary intraocular pressure elevation in eyes with intraocular tumors. Ophthalmology 94:839, 1987.
7. Walton, D. S., and Grant, W. M.: Retinoblastoma and iris neovascularization. Am. J. Ophthalmol. 65:598, 1968.
8. Howard, G. M.: Spontaneous hyphema in infancy and childhood. Arch. Ophthalmol. 69:583, 1968.
9. Stafford, W. R., Yanoff, M., and Posnell, B.: Retinoblastoma initially misdiagnosed as primary ocular inflammation. Arch. Ophthalmol. 82:771, 1969.
10. Andrew, J. A., and Smith, D. R.: Unsuspected retinoblastoma. Am. J. Ophthalmol. 60:536, 1965.
11. Sezer, N., and Bernishak, R.: The diagnosis of retinoblastoma. Ophthalmologica 151:184, 1966.
12. Schuster, S. A. D., and Ferguson, E. C.: Unusual presentation of retinoblastoma. South. Med. J. 63:4, 1970.
13. Rozansky, N. M.: A necrotic retinoblastoma simulating panophthalmitis. Surv. Ophthalmol. 9:381, 1964.
14. Johnson, T. E., Senft, S. H., Nasr, A. M., Gudmund, B., and Cavender, J. C.: Pediatric orbital tumors in Saudi Arabia. Orbit 9:205, 1990.
15. Rootman, J., and Ellsworth, R. M.: Orbital extension of retinoblastoma. A clinicopathological study. Can. J. Ophthalmol. 13:72, 1978.
16. Ellsworth, R.: Orbital retinoblastoma. Trans. Am. Ophthalmol. Soc. 72:79, 1974.

Marked Intraocular Pressure Response to Instillation of Corticosteroids in Children

Masahito Ohji, M.D., Shigeru Kinoshita, M.D., Emiko Ohmi, M.D.,
and Yasuaki Kuwayama, M.D.

We examined intraocular pressures of patients with strabismus whose eyes were instilled with corticosteroid eyedrops after a strabismus operation. Group A consisted of 11 children under 10 years of age whose eyes were instilled with 0.1% dexamethasone; Group B consisted of nine patients 10 years old or older whose eyes were instilled with 0.1% dexamethasone; and Group C consisted of 13 children under 10 years of age whose eyes were instilled with 0.1% fluorometholone. In Group A, four patients had intraocular pressures greater than 30 mm Hg, five had intraocular pressures from 21 to 30 mm Hg, and two had intraocular pressures under 21 mm Hg one or two weeks postoperatively. The intraocular pressure decreased to less than 21 mm Hg one week after discontinuation of dexamethasone treatment in all nine patients. No patients in Groups B or C had intraocular pressures greater than 20 mm Hg. Our results suggest that marked ocular hypertensive response to 0.1% dexamethasone treatment occurs frequently in children under 10 years of age.

CORTICOSTEROIDS (administered as eyedrops, ointment, or used systemically) are commonly and frequently used as anti-inflammation drugs and are indispensable in treating inflammatory eye diseases. Corticosteroids have many side effects, such as cataracts and glaucoma. Corticosteroid-induced glaucoma is one of the most serious side effects because the loss of the visual field is irreversible. Moreover, corticosteroid-induced glaucoma is not uncommon, especially with topical corticosteroid use.[1] About one third of normal subjects have been found to respond to corticosteroids.[2,3] Age is an important factor in the response of intraocular pressure to treatment with corticosteroids. Armaly[4,5] reported that intraocular pressure increases more frequently in people aged 40 years or more than it does in people aged 18 to 30 years after instillation of 0.1% dexamethasone eyedrops. Several cases of corticosteroid-induced glaucoma in children have been reported and some cases diagnosed as congenital glaucoma may actually have been corticosteroid-induced.[6] To evaluate the response of intraocular pressure in children under 10 years of age to treatment with corticosteroids, we investigated the intraocular pressures in children who had received dexamethasone eyedrops after a strabismus operation.

Subjects and Methods

We investigated the intraocular pressures of patients who received corticosteroid eyedrops after a strabismus operation. The subjects in this study consisted of 33 Japanese patients whose intraocular pressures were measured one or two weeks after the operation. We divided the patients into three groups. Group A consisted of 11 patients all less than 10 years old (aged 3 to 8 years; mean, 5.5 years), who underwent strabismus operations in the period of July 1989 to June 1990. Group B comprised nine patients aged 10 years or older (aged 12 to 49 years; mean, 20.6 years), who underwent strabismus operations in the period of July 1989 to September 1990. Group C consisted of 13 children all less than 10 years old (aged 3 to 9 years; mean, 6.5 years), who underwent strabismus operations in the period of July 1990 to September 1990. Patients of Groups A and B

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received 0.1% dexamethasone eyedrops and patients of Group C received 0.1% fluorometholone eyedrops. The instillation was performed three times daily. Treatment began the day after the operation and was continued for at least two weeks, except in patients whose intraocular pressures increased to 28 or more mm Hg one week after the operation. In patients on whom bilateral operations were performed or who received bilateral instillation of eyedrops, the intraocular pressure of the right eye was used for analysis. Intraocular pressures one week after the operation were used in patients whose intraocular pressure was measured at both one and two weeks after the operation.

Intraocular pressures of patients who were 6 years old or older were measured using a Goldmann applanation tonometer. Six of 11 patients in Group A, nine of nine patients in Group B, and eight of 13 patients in Group C were 6 years of age or older. Because of technical difficulties, the intraocular pressures of children under 6 years of age were measured with a noncontact tonometer (Topcon, Tokyo, Japan).

The different types of strabismus operations performed in this study were the following: resection of medial rectus muscle or lateral rectus muscle; and recession of medial rectus muscle, lateral rectus muscle, superior rectus muscle, or inferior oblique muscle. No eyes underwent more than two types of operations. No distinct differences in the distribution of the different types of operations were observed among each group. All operations on children less than 10 years old were performed while the child was under general anesthesia and all operations on patients 10 years old or older were performed while the patient was under local and retrobulbar anesthesia.

Results

Intraocular pressure—Of the 11 children in Group A, five had intraocular pressures greater than 30 mm Hg, four had intraocular pressures between 21 and 30 mm Hg, and two had intraocular pressures below 21 mm Hg, after the instillation of 0.1% dexamethasone (Figure). The intraocular pressures of the nine patients who had intraocular pressures greater than 20 mm Hg decreased to under 21 mm Hg one week after discontinuation of treatment with dexamethasone. The intraocular pressures of all the patients in Group B ranged from 9 to 20 mm Hg, and from 10 to 20 mm Hg in Group C one or two weeks after the operation.

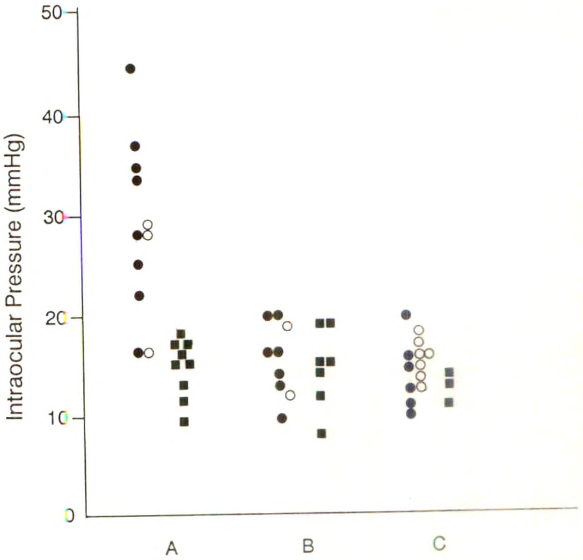

Figure (Ohji and associates). Intraocular pressure measured one week (solid circles) or two weeks (open circles) after surgery, and four or more weeks after discontinuation of corticosteroid treatment (solid squares). Group A included children less than 10 years old, whose eyes were instilled with 0.1% dexamethasone; Group B included patients 10 years old or older, whose eyes were instilled with 0.1% dexamethasone; and Group C included children less than 10 years old, whose eyes were instilled with 0.1% fluorometholone.

Intraocular pressures of nine patients in Group A, seven patients in Group B, and three patients in Group C were also measured four or more weeks after discontinuation of treatment with corticosteroids. The intraocular pressures were under 21 mm Hg in all patients.

Intraocular pressures of contralateral, unoperated-on and uninstilled eyes were under 21 mm Hg in all patients one or two weeks after the operation and four or more weeks after discontinuation of treatment with corticosteroids.

Increase in intraocular pressure—In patients whose eyes were instilled with 0.1% dexamethasone, the intraocular pressure increase was calculated by subtracting the baseline intraocular pressures from intraocular pressures measured either one or two weeks postoperatively. Intraocular pressures four or more weeks after cessation of corticosteroid administration were used as the baseline intraocular pressures. The baseline intraocular pressure was not measured for two children in Group A and two patients in Group B.

Nine children in Group A had increased intraocular pressures of 7 to 29 mm Hg above baseline intraocular pressure. Seven patients in Group B had increased intraocular pressures of −1 to 5 mm Hg above baseline intraocular pressure. Armaly[2] classified patients who responded to corticosteroid treatment into three grades on the basis of change in intraocular pressure after a four-week, three-times-a-day instillation of dexamethasone. The intraocular pressure change in patients with low responses was under 6 mm Hg. The intraocular pressure change in patients with intermediate responses was from 6 to 15 mm Hg and was over 15 mm Hg in patients with high responses. Applying Armaly's classification to Group A, none of nine patients had low responses, five of nine (56%) had intermediate responses, and four of nine (44%) had high responses. Seven of seven patients (100%) had low responses and no patients had intermediate or high responses in Group B. Children less than 10 years old had fewer low responses than did patients who were 10 years of age or older ($P < .001$; Table).

Bilaterally instilled eyes—Six children in Group A underwent operations and bilateral instillation of dexamethasone. Five of the six patients had intraocular pressures higher than 25 mm Hg bilaterally. The intraocular pressures of the sixth patient were 16 mm Hg in the right eye and 17 mm Hg in the left eye. The differences in intraocular pressures between right eyes and left eyes were within 2 mm Hg in four of the patients, 5 mm Hg in one patient, and 7 mm Hg in one patient. Three of nine patients in Group B and 11 of 13 patients in Group C also underwent operations and bilateral instillation of corticosteroids. All the eyes in Group B and Group C had an intraocular pressure of less than 21 mm Hg one or two weeks after onset of instillation.

An 8-year-old boy underwent a unilateral strabismus operation and had both his operated-on eye and unoperated-on eye instilled with 0.1% dexamethasone by mistake. The intraocular pressure of his operated-on eye was 22 mm Hg and the intraocular pressure of the unoperated-on fellow eye was 28 mm Hg one week after the operation.

TABLE
INTRAOCULAR PRESSURE RESPONSE TO 0.1% DEXAMETHASONE INSTILLATION

INCREASE IN INTRAOCULAR PRESSURE	GROUP A (< 10 YEARS OLD)	GROUP B (≥ 10 YEARS OLD)
Low response ≤ 5 mm Hg	0*	7*
Intermediate response 6–15 mm Hg	5	0
High response ≥ 16 mm Hg	4	0

*$P < .001$ with Fisher's exact *t*-test.

Discussion

Previously, 0.1% dexamethasone eyedrops were used to prevent inflammation after operations such as a strabismus operation. Treatment was changed to the use of 0.1% fluorometholone eyedrops in children after intraocular pressures were observed to increase frequently in eyes that received dexamethasone instillation after the operation. Therefore, the eyes of children less than 10 years old who underwent a strabismus operation before June 1990 were instilled with dexamethasone eyedrops and the eyes of children less than 10 years old who underwent an operation after July 1990 were instilled with fluorometholone eyedrops.

Of 11 children in Group A, nine had increased intraocular pressures. All eyes with intraocular pressures greater than 20 mm Hg received dexamethasone treatment and underwent subsequent decrease in intraocular pressure if this treatment was discontinued. Therefore, the increase in intraocular pressure seems to have been induced by the instillation of dexamethasone, not by muscle retraction or measuring error (including the squeezing of any painful eyes after a strabismus operation). Furthermore, none of the 13 children in Group C (who were under 10 years of age and whose eyes were instilled with 0.1% fluorometholone after the same operation) had an increase in intraocular pressure. Therefore, it is reasonable to conclude that all the increased intraocular pressures observed in the children after the strabismus operation were induced by the instillation of dexamethasone.

As we have shown, a larger population of children under 10 years of age had increased intraocular pressures after instillation of 0.1%

dexamethasone, compared with adult patients in Group B and previous reports.[2,3] Additionally, some of the children under 10 years of age had increased intraocular pressure as early as one week after the onset of instillation. The type of operation, the presence of strabismus, and race or age may be related to the cause of these differences. Strabismus is presumed not to be the sole cause because no patients in Group B had increases in intraocular pressure. The intraocular pressures of adult white and Japanese patients also did not differ.[2,7] The operation was not considered to be the cause because no patients in Groups B and C had increased intraocular pressures after the same operation. Operation-induced alteration in the rate of dexamethasone penetration into the eye might cause a more frequent and quicker increase in intraocular pressure. However, the alteration is presumed not to be the main cause of the intraocular pressure increase because patients who were 10 years of age or older did not have intraocular pressure increase after the same treatment. Additionally, the eye that was not operated on but was mistakenly instilled with dexamethasone also had increased intraocular pressure after instillation of dexamethasone. Therefore, the subject's age is presumably the cause of the difference.

Some cases of dexamethasone-induced ocular hypertension in children have been reported. In one report involving statistical analysis of response to corticosteroid treatment in children, the intraocular pressures of children with vernal conjunctivitis who were from 4 to 19 years old (mean, 9.7 years) were examined.[8] The hypertensive response to corticosteroid instillation in children was reported to be lower than that in adults. These findings are in direct contrast to our report. Some possible explanations for the difference in results include the following: difference in age, the presence of vernal conjunctivitis or strabismus, past use of corticosteroids, operation, or race. As mentioned previously, strabismus and race are presumed not to be the cause. The operation-induced alteration in the rate of dexamethasone penetration into the eye might result in intraocular pressure increase, although this is supposed to be unlikely as previously mentioned. The possibility cannot be ruled out that the response to dexamethasone increases after general anesthesia is achieved in the patient. Vernal conjunctivitis and past use of corticosteroids remain as possible causes.

Because only one third of adults respond to corticosteroid treatment, at least two thirds of the children in Group A will have low or no responses at maturity. Immaturity in the trabecular meshwork function may be the cause of the high percentage of children who respond to corticosteroid treatment. Similarly, Reme and Lalive d'Epiphany[9] reported that chamber angle components were fully present at birth, with the maturation of angle cellular and extracellular components observed one to eight years after birth. This report corresponds very well with our results because two 12-year-old patients in Group B had no increase in intraocular pressure.

In a rabbit model, 100% of the younger rabbits had intraocular pressure increase after receiving dexamethasone eyedrops, whereas no intraocular pressure increase was observed in dexamethasone-treated older rabbits.[10] This report also corresponds very well with our results.

Different corticosteroids have different intraocular pressure–increasing potential[7,11,12]; for example, dexamethasone and betamethasone have a higher potential than does fluorometholone. None of the children in our report had an intraocular pressure increase using 0.1% fluorometholone. Although the use of fluorometholone is thought to be much safer than the use of dexamethasone in children, intraocular pressure may increase with extended instillation of fluorometholone. Intraocular pressure must be monitored closely when corticosteroids are used (especially with topical use) and intraocular pressure should be measured and checked more frequently in children.

References

1. Hodapp, E. A., and Kass, M. A.: Corticosteroid-induced glaucoma. In Ritch, R., and Shields, M. B. (eds.): The Secondary Glaucomas. St. Louis, C. V. Mosby, 1982, pp. 258–265.

2. Armaly, M. F.: Statistical attributes of steroid hypertensive response in the clinically normal eye. Invest. Ophthalmol. 4:187, 1965.

3. Becker, B.: Intraocular pressure response to topical corticosteroids. Invest. Ophthalmol. 4:198, 1965.

4. Armaly, M. F.: Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. Arch. Ophthalmol. 70:482, 1963.

5. ———: Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. Arch. Ophthalmol. 70:492, 1963.

6. Kass, M. A., Kolker, A. E., and Becker, B.: Chronic topical corticosteroid use simulating congenital glaucoma. J. Pediatr. 81:1175, 1972.

7. Kitazawa, Y.: Increased intraocular pressure induced by corticosteroids. Am. J. Ophthalmol. 82:492, 1976.

8. Biedner, B. Z., David, R., Grudsky, A., and Sachs, U.: Intraocular pressure response to corticosteroids in children. Br. J. Ophthalmol. 64:430, 1980.

9. Reme, C., and d'Epinay, S. L.: Periods of development of the normal human chamber angle. Doc. Ophthalmol. 51:241, 1981.

10. Knepper, P. A., Weinstein, H. G., and Black, L. J.: Intraocular pressure and glycosaminoglycan distribution in the rabbit eye. Effect of age and dexamethasone. Exp. Eye Res. 27:567, 1978.

11. Podos, S. M., Krupin, T., Asseff, C., and Becker, B.: Topically administered corticosteroid preparations. Comparison of intraocular pressure effects. Arch. Ophthalmol. 86:251, 1971.

12. Fairbairn, W. D., and Thorson, J. C.: Fluorometholone. Arch. Ophthalmol. 86:138, 1971.

OPHTHALMIC MINIATURE

He frees the noose and lays the wretched woman down, then—O hideous sequel!—rips from off her dress the golden brooches she was wearing, holds them up, and rams them home right through the eyes. "Wicked, wicked eyes!" he gasps, "You shall not see me nor my shame—not see my present crime. Go dark, for all time blind to what you never should have seen, and blind to those this heart has cried to see." And as this dirge went up so did his hands to strike his founts of sight, not once but many times. And all the while his eyeballs gushed in bloody dew upon his beard . . . no, not dew, no oozing drops—a spurt of black-ensanguined rain like hail beat down.

Sophocles; Roche, Paul (trans.) *Oedipus the King*
New York, New American Library, 1958, p. 73

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EDITORIAL

The American Board of Ophthalmology Turns 75

William H. Spencer

On May 8, 1916, the American Board for Ophthalmic Examinations, the predecessor of the American Board of Ophthalmology, was established in Memphis, Tennessee. Its first written test was given at the University of Tennessee College of Medicine on Dec. 13, 1916. The next day another written test was followed by an oral examination. Seven candidates passed and three failed. Thus began the voluntary process of certifying physicians as medical specialists, a process that was gradually adopted by all of American medicine and has since played a large part in shaping the graduate education requirements for physicians in this country. The Board was incorporated on May 3, 1917, and in 1933 its name was officially changed to the American Board of Ophthalmology.

The Board was established at a time when the medical profession was almost totally self-regulated, and physicians had the freedom to decide personally whether or not their education and professional skills were of adequate quality to practice competently a particular specialty. Unfortunately, not all were well qualified. Medical school training was erratic, and no defined course of postgraduate study was provided in any specialty of medicine. The founding members of the Board hoped to protect the public from exploitation by physicians who claimed to have the knowledge and ability to treat ocular diseases but actually had little or no formal training. They intended to establish educational and testing standards that would reassure a patient that a diplomate of the Board was professionally qualified.

The goal was laudable, but the gestation period was long. The concept of a specialty examining board was untried, and many practicing physicians were critical of the idea. Such a qualification had been championed by Edward Jackson for almost a decade before the first examination was given. He was joined by other leaders in ophthalmology, including Derrick T. Vail, Sr., who publicly proposed the idea in his 1908 presidential address to the

American Academy of Ophthalmology and Otolaryngology. Consensus was finally reached in 1915 with approval of the report of a joint committee composed of members representing the American Academy of Ophthalmology and Otolaryngology, the Section of Ophthalmology of the American Medical Association, and the American Ophthalmological Society. The organizational model, which utilized existing established ophthalmologic organizations as "parents" of the Board, subsequently served as the prototype structure for boards in other specialties.

By 1932, three additional boards had been founded (Otolaryngology, Obstetrics and Gynecology, and Dermatology and Syphilology). In 1933, the Advisory Board for Medical Specialties (later the American Board of Medical Specialties) was formed to discuss common problems, to coordinate the work of boards, and to improve postgraduate medical education. In the ensuing 58 years the number of member boards of the American Board of Medical Specialties increased to 23. A gradual process of growth and development has resulted in a serviceable but somewhat complex system of accrediting new boards, which encompasses every aspect of medicine. Individual specialty boards participate as separate entities and are accountable to several overseeing medical organizations concerned with the evaluation of medical education and the maintenance of high-quality patient care. The success of the system depends upon its credibility to the public as well as to third-party payers and to state and federal governmental authorities. It requires the continued support of all physicians if it is to flourish and remain within the province of the profession.

The diplomates of the American Board of Ophthalmology have provided it with strong support throughout its existence. Each year it benefits from the contributions of a large number of ophthalmologists in all types of practice who serve without remuneration as associate examiners for the oral examination. Others aid in the development of questions for the Written Qualifying Examination. This demonstration of support is fully appreciated by members of the Board and its staff, who recognize the increasing demands on their time and economic pressures that affect all practitioners and the faculties of academic training programs. One might logically ask how long such altruistic assistance can continue. It is heartening to report that during the past year all associate examiners surveyed voted to continue to pay their own expenses to participate in the oral examinations. Each was aware of the financial burden that most Board candidates face and recognized that application fees of candidates were the only source of Board income. These fees would have to be raised considerably to compensate the expenses of the associate examiners.

The Board approaches its 76th year at a time when the entire scope of medical practice is undergoing a rapid and profound change combined with a growing public concern about the accountability of the medical profession. The Board has long recognized its moral obligation to heed the concerns of patients, who expect practicing ophthalmologists to maintain their knowledge and skills. It has been mindful of the concerns of ophthalmologists about state and federal legislative plans to require periodic relicensure and recredentialing. To meet the expectations of the public, legislative requirements, and the needs of ophthalmologists, the Board will begin to issue certificates limited to ten years to diplomates certified in 1992 and thereafter. The Board will also provide a mechanism to permit current diplomates to renew their certificates if they reside in a state where periodic relicensure is required.

It is difficult, if not impossible, to codify the qualities that go into the making of a competent practitioner. Such factors are far more likely to be recognized and confirmed by practicing physicians than by any government agency. The task faced by every American Board is to develop and to administer a reliable, credible, clinically relevant, and reasonable certificate renewal process that will be cost effective and will not penalize Board diplomates. The process must stress continuous improvement of knowledge and proficiency. The Board recognizes the complexity of the task and the need to provide a variety of flexible pathways that will provide a practical process.

As we near the end of the 20th century, the original intent of the Board's founders has been largely accomplished. Ophthalmology residency training is outstanding, and the initial certification process validates the educational background and training of new diplomates. The certificate renewal program will soon enable diplomates to demonstrate their continued commitment to the acquisition and application of new knowledge and skills required for clinical excellence.

The pioneering ophthalmologists who conceived and initiated the American Board of Ophthalmology and those who nurtured it during the past 75 years deserve our profound respect and gratitude. Their efforts have resulted in a strong Board that is well prepared for future challenges.

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LETTERS TO THE JOURNAL

Rhegmatogenous Retinal Detachment After Initiation of Ocusert Therapy

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Although the existence of a causal relationship between miotic use and retinal detachment has never been unequivocally proven or universally agreed upon, there is strong anecdotal evidence to suggest such a relationship.[1-3] A recent survey of general ophthalmologists, retina specialists, and glaucoma specialists demonstrated that a majority of all three groups believes such a relationship does exist.[3] It has been suggested that if miotic use is essential, "the weakest effective miotic agent, including Ocusert pilocarpine where feasible, is preferred."[2] We recently encountered a patient who developed retinal detachment shortly after initiating therapy with Ocusert pilocarpine.

A 36-year-old, phakic man with pigmentary glaucoma was referred for treatment of uncontrolled intraocular pressure. There was no family history of retinal detachment and he denied any visual symptoms. Previous antiglaucoma therapy consisted of timolol maleate only. He had never been treated with miotics. His refractive error was −1.25 sph. in the right eye and −3.00 sph. in the left eye. Axial lengths were 24.0 mm in the right eye and 24.5 mm in the left eye. Indirect ophthalmoscopy without scleral depression disclosed typical lattice degeneration in both eyes without retinal breaks. Therapy was begun with Ocusert Pilo-20, changed every five days in each eye. The patient was seen four weeks later at which time he was again asymptomatic. Repeat examination by indirect ophthalmoscopy disclosed an inferotemporal retinal detachment in the left eye extending posterior to the equator but not to the vascular arcades. The causative break was a round hole in a lattice lesion.

Retinal detachments can be considered to be potentially miotic-induced if the duration of miotic use before development of the detachment is not greater than two months.[1] All types of miotic eyedrops have been incriminated in this process, but many believe the stronger miotics are more likely to cause retinal detachments.[3] Animal studies have demonstrated that administration of Ocusert results in constant low levels of pilocarpine in the ciliary body and iris, whereas in order to attain the same trough tissue levels with eyedrop therapy, a peak tissue level three to five times as great is required (Ocusert, package insert).

We found another published report of a retinal detachment that was discovered after the initiation of Ocusert therapy.[4] The patient had been treated with other miotics previously and no fundus examination was performed before switching treatment to Ocusert therapy, thus casting doubt on the relationship between the

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two events. Interestingly, that patient also had pigmentary glaucoma.

The mechanism of miotic-induced retinal detachment has never been elucidated. There has been some controversy as to whether miotics cause new retinal breaks through anterior movement of the ciliary body or increased vitreoretinal traction, or if miotics induce retinal detachment in eyes that have pre-existing breaks.[3] While no breaks were seen when our patient was first examined, because the causative break was an atrophic hole and not a tractional break supports the view that the abnormality was present at the time of initial examination and was not found because scleral depression was not performed. However, this cannot be proven. It has been reported that miotic treatment can induce a new retinal break after careful retinal examinations failed to find any abnormality before the institution of treatment.[1]

Well-known risk factors for the development of retinal detachment in our patient include myopia and lattice degeneration. The increased risk of retinal detachment in patients with pigmentary glaucoma and the pigment dispersion syndrome is not as widely appreciated, and appears to occur with equal frequency in patients using and not using miotics.[5] The need for careful examination of the peripheral fundus in patients with any of these risk factors before the initiation of miotic therapy cannot be overemphasized. Inasmuch as our patient developed a retinal detachment after starting Ocusert therapy in the absence of a peripheral fundus lesion that would be treated by most retinal surgeons, we recommend that careful fundus examinations be repeated shortly after the initiation of therapy, regardless of the strength of the prescribed miotic agent.

References

1. Pape, L. G., and Forbes, M.: Retinal detachment and miotic therapy. Am. J. Ophthalmol. 85:558, 1978.

2. Ackerman, A. L.: Retinal detachments and miotic therapy. In Pruett, R. L., and Regan, C. D. J. (eds.): Retina Congress. New York, Appleton-Century-Crofts, 1972, pp. 533–539.

3. Kraushar, M. F., and Steinberg, J. A.: Miotics and retinal detachment. Upgrading the community standard. Surv. Ophthalmol. 35:311, 1991.

4. Puustjarvi, T.: Retinal detachment during glaucoma therapy. Ophthalmologica 190:40, 1985.

5. Scheie, H. G., and Cameron, J. D.: Pigment dispersion syndrome. A clinical study. Br. J. Ophthalmol. 65:264, 1981.

Mixing Fortified Antibiotic Eyedrops

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A recent article on the stability of custom-made fortified antibiotic eyedrops[1] illustrates several problems with this therapy. Usually these mixtures are made without the addition of any stabilizers or preservatives. Often, the pharmacist will be unsure of just what diluent in which to add the intravenous antibiotic in order to obtain the desired final concentration.

Additionally, it may be desirable to be able to vary the antibiotic concentration to the clinical situation because increasing toxicities are observed with increasing concentrations.[2] As pharmacists spend more of their time dispensing prepackaged medications, the potential problems in having them mix special formulas increase. Another potential problem, often not considered, is in the choice of an appropriate container in which to dispense a preparation intended for topical, ocular application.

For fortified gentamicin (or tobramycin) eyedrops, all these problems can be resolved by specifying a distinct recipe to the pharmacist. Simply adding the intravenous antibiotic to the commercially available eyedrop has advantages. First, the mixture already contains stabilizers and preservatives known to be compatible with and appropriate for the antibiotic. Second, the mixture will be given to the patient in a container specifically designed to store and dispense eyedrops.

The calculations are straightforward. Gentamicin is available as a commercial eyedrop as 5 ml in a concentration of 3 mg/ml. Thus, the mixture contains 15 mg. Intravenous gentamicin is available in a concentration of 40 mg/ml. Thus, adding 1 ml of the intravenous mixture to the bottle results in 55 mg in 6 ml or 11.5 mg/ml. Adding 2 ml results in 95 mg in 7 ml or 13.6 mg/ml. Adding 2.5 ml results in 115 mg in 7.5 ml or 15.3 mg/ml.

Specifying the composition of the fortified antibiotic eyedrops in this manner has several advantages. The medications will be dispensed in a container specifically designed for the purpose. Preservatives and stabilizers will be retained. It is easier to maintain sterility through these relatively simple maneuvers. Finally, there is no confusion as to the nature of the diluent to be used.

In this way, fortified antibiotics may be dispensed to the patient in less time, with less chance for pharmaceutical error, with more chemical stability, and in an appropriate container for optimum patient compliance.

References

1. Bowe, B. E., Snyder, J. W., and Eiferman, R. A.: An in vitro study of the potency and stability of fortified ophthalmic antibiotic preparations. Am. J. Ophthalmol. 111:686, 1991.
2. Davison, C. R., Tuft, S. F., and Dart, J. K. G.: Conjunctival necrosis after administration of topical fortified aminoglycosides. Am. J. Ophthalmol. 111:690, 1991.

Tuberculous Choroiditis Diagnosed By Chorioretinal Endobiopsy

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Treatment of inflammatory posterior segment disorders is often compromised by the inability to make a definitive diagnosis. We recently treated a patient with progressive bilateral chorioretinitis of unknown origin. A pars plana vitrectomy with chorioretinal endobiopsy helped establish a diagnosis of tuberculous chorioretinitis.

A 56-year-old healthy man had a ten-day history of painless visual loss in his right eye. Visual acuity was R.E.: counting fingers and L.E.: 20/25. Mild cellular reaction was present in the anterior chambers and vitreous cavities bilaterally. Multiple hemorrhagic, yellow-white chorioretinal infiltrates were seen in the posterior pole of the right eye and midperiphery of both fundi (Fig. 1). Fluorescein angiography showed early hypofluorescence of the lesions and mild, late staining. Results of systemic examination were unremarkable. Blood cell count, serum chemistry, erythrocyte sedimentation rate, angiotensin-converting enzyme, syphilis serology, viral titers, toxoplasmosis titer, intradermal purified protein derivative, and chest roentgenogram provided no positive findings. Our presumptive diagnosis was acute retinal necrosis, and the patient was treated with a one-week course of acyclovir intravenously (750 mg every eight hours), which appeared to stabilize the lesions. After two further weeks the lesions in the right eye reactivated. New infiltrates appeared near the left fovea despite a second course of acyclovir, threatening central vision in the better eye. Chorioretinal biopsy of the right eye was recommended to help establish a diagnosis.

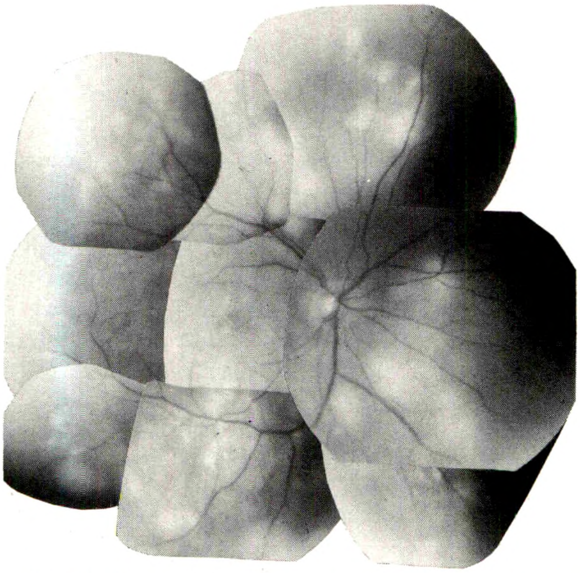

Fig. 1 (Barondes and associates). Photographic montage of the right eye showed scattered chorioretinal infiltrates in the midperiphery and posterior pole.

A standard three-port vitrectomy technique was used. An intraoperative Gram stain of the vitreous aspirate showed no organisms. After complete vitrectomy, a relatively avascular site in the superior hemisphere with an active lesion was selected for biopsy. An encircling ring of endodiathermy (pulsed, unimanual bipolar) with an inner diameter of approximately 3 mm was applied to the retina until full-thickness chorioretinal separation was achieved. Adhesions between the biopsy specimen and the adjacent tissue were incised, and the biopsy

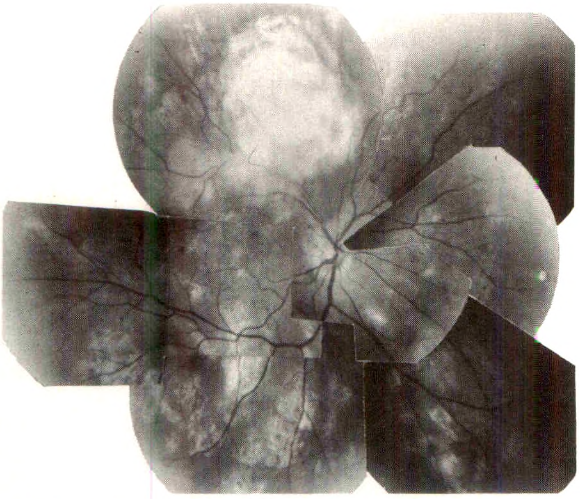

Fig. 2 (Barondes and associates). Photographic montage of the right eye at the five-month postoperative visit. There was tractional distortion of the macula because of an epiretinal membrane at the biopsy site.

button was elevated from the underlying sclera. The specimen was bisected in situ to facilitate removal through an enlarged sclerotomy. Endolaser photocoagulation was applied around the biopsy site. Minor bleeding was treated by raising the infusion bottle and applying additional endodiathermy. An automated air-fluid exchange was performed, followed by an air-gas (20% perfluoropropane) exchange. At the conclusion of the procedure the retina was flat and there was no bleeding.

The specimen showed necrotic inner retina, thickened choroid, giant cells, and a diffuse lymphocytic infiltrate. Ziehl-Neelsen's staining of the tissue homogenate demonstrated acid-fast bacilli. Postoperative treatment with antituberculous medications resulted in gradual resolution of the choroiditis over a period of three months. The retina and choroid remained attached during the six-month postoperative observation period, with retention of reading vision in the left eye (20/40) and improvement in the vision of the right eye (20/70), despite the development of an epiretinal membrane with macular traction (Fig. 2).

Transscleral and transvitreal approaches to obtain choroidal and retinal tissue have been described.[1] Tumor cells suitable for cytologic examination have been removed by endobiopsy[2,3] and by transvitreal needle aspiration.[4] Endobiopsy of detached retina has provided tissue suitable for histopathologic examination.[5] Our technique differs in that it provided tissue from attached retina and choroid. The safety and efficacy of endobiopsy techniques merit further study.

References

1. Peyman, G. A., Raichand, M., and Schulman, J.: Diagnosis and therapeutic surgery of the uvea. I. Surgical technique. Ophthalmic Surg. 17:822, 1986.

2. Peyman, G. A., and Cohen, S. B.: Ab interno resection of uveal melanoma. Int. Ophthalmol. 9:29, 1986.

3. Fastenberg, D. M., Finger, P. T., Chess, Q., Koizumi, J. H., and Packer, S.: Vitrectomy retinotomy aspiration biopsy of choroidal tumors. Am. J. Ophthalmol. 110:361, 1990.

4. Jakobiec, F. A., Coleman, D. J., and Chattock, A.: Ultrasonically guided needle biopsy and cytologic diagnosis of solid intraocular tumors. Ophthalmology 86:1662, 1979.

5. Freeman, W. R., Wiley, C. A., Gross, J. G., Thomas, E. L., Rao, N. A., and Liggett, P. E.: Endoretinal biopsy. Indications, utility and techniques. Ophthalmology 96:159, 1989.

Granulomatous Uveitis and Quinidine Hypersensitivity

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Although quinidine hypersensitivity has been reported to cause granulomatous uveitis[1,2] and histopathologically proven granulomatous hepatitis,[3-5] quinidine hypersensitivity is not commonly included in the differential diagnosis of granulomatous uveitis.

An 81-year-old woman was referred because of acute, bilateral reduction of her vision. Visual acuity was R.E.: 20/80 and L.E.: 20/200. She had bilateral corneal edema and intraocular pressure of 50 mm Hg in each eye. Biomicroscopic examination disclosed bilateral diffuse microcystic corneal edema and ten to 15 mutton fat keratic precipitates on each cornea. Three tan, round, and well-circumscribed nodules were scattered on the margin of the left iris. There was entropion of the iris pigment epithelium in both eyes but no posterior synechiae. Gonioscopy through the hazy cornea showed open angles without peripheral anterior synechiae. There were possible small sessile tan nodules on the superior surface of each iris. Her fundi were normal.

Prednisolone acetate ophthalmic suspension 1.0% four times daily and betaxolol 0.5% ophthalmic solution twice daily was initiated in both eyes. Methazolamide, 25 mg twice a day orally, was also begun. On the following morning the intraocular pressure was 38 mm Hg in the right eye and 32 mm Hg in the left eye. The keratic precipitates and iris nodules were smaller. Six days later the intraocular pressure was 18 mm Hg in the right eye and 15 mm in the left eye. A few small keratic precipitates remained but all iris nodules had resolved.

Her primary physician stated that seven weeks earlier, she had been seen because of palpitations, and quinidine gluconate, 324 mg twice a day, was prescribed. Two weeks later, palpitations had stopped but the patient had had a fever, headache, and generalized weakness for one week. A viral syndrome was diagnosed, and amantadine, 100 mg twice daily, was prescribed. Cefixime treatment for a presumed sinus infection that had been diagnosed elsewhere was continued. Four days later she returned with hives, fevers of up to 101 F, decreased appetite, and loose stools. Laboratory studies disclosed mild anemia and increased liver enzymes. The cefixime and amantidine were discontinued.

Her rapid plasma reagin and fluorescent treponemal antibody-absorption were nonreactive. A purified protein derivative was nonreactive but the *Candida* sp. control was positive. A chest x-ray showed no evidence of sarcoid or tuberculosis. Angiotensin-converting enzyme was mildly increased.

A presumptive diagnosis of quinidine hypersensitivity was made and within one week of stopping quinidine, her constitutional symptoms resolved. Three weeks after the onset of ocular symptoms, she had no keratic precipitates and her intraocular pressure, with no ocular medications, was 16 mm Hg in the right eye and 14 mm Hg in the left eye. Her visual acuity was 20/50, which was consistent with her nuclear lens opacities.

The evidence for quinidine hypersensitivity as a cause for granulomatous anterior uveitis and glaucoma is circumstantial. This patient's syndrome of fever, headache, urticaria, malaise, increased liver enzymes, decreased hearing, mild anemia, and diarrhea beginning within four weeks of quinidine therapy are consistent with quinidine hypersensitivity. The occurrence of a granulomatous uveitis with these constitutional symptoms and the lack of clinical history and data confirming any of the classic causes for granulomatous uveitis support quinidine hypersensitivity as the cause of uveitis.

Histopathologic studies show that quinidine hypersensitivity causes granulomatous inflammation in the liver.[3-5] Epithelioid cell granulomas with occasional lymphocytes have been found in liver biopsy specimens of patients with known quinidine-induced hepatitis. Further proof of the association between quinidine hypersensitivity and granulomatous uveitis in this patient would require rechallenge with quinidine. The patient has, however, understandably declined.

References

1. Spitzberg, D. H.: Acute anterior uveitis secondary to quinidine sensitivity. Arch. Ophthalmol. 97:1993, 1979.
2. Fraunfelder, F. T.: Drug-Induced Ocular Side Effects and Drug Interactions, ed. 3. Philadelphia, Lea & Febiger, 1989, pp. 264–265.
3. Chajek, T. Lehrer, B., Geltner, D., and Levij, I. S.: Quinidine-induced granulomatous hepatitis. Ann. Intern. Med. 81:774, 1974.
4. Bramlet, D. A., Posalaky, Z., and Olson, R.: Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. Arch. Intern. Med. 140:395, 1980.
5. Knobler, H., Levij, I. S., Gavish, D., and Chajak-Shaul, T.: Quinidine-induced hepatitis. Arch. Intern. Med. 146:526, 1986.

Prevalence of Lyme Disease Among Patients With Uveitis

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Lyme disease, a spirochetal infection spread by tick bites, has recently been recognized as a cause of uveitis.[1] The prevalence of Lyme disease among patients with uveitis is unknown.

To determine the prevalence of Lyme disease among patients with uveitis, we performed an ELISA assay[2] for IgM or IgG antibodies to the Lyme spirochete, using sera on 84 patients with uveitis. The patients included 31 individuals with an established diagnosis (11 with ankylosing spondylitis, 12 with Reiter's syndrome, and eight with sarcoidosis), 14 individuals with pars planitis, and 39 with uveitis of unknown cause. All patients were examined at the uveitis clinic of the Oregon Health Sciences University. A positive IgG titer (≥ 200 units) was found in sera from one patient with Reiter's disease and one with uveitis of unknown cause. Two patients with uveitis of unknown cause had significant IgM antibodies detected, but despite longstanding disease, their IgG antibody titers were negative. All sera with titers greater than 200 units were further studied by Western blot analysis. In no instance did the Western blot confirm the presence of antibody specific for a Lyme-disease-related antigen. This supports the likelihood that the serologic results represent a false-positive.[3] Intermediately positive IgM or IgG titers were found in 20% to 30% of patients who were equally distributed among all patient groups.

We suggest that a test demonstrating antibody to the Lyme spirochete should be interpreted cautiously in uveitis patients from a nonendemic area. Current commercially available laboratory tests for antibody to *Borrelia burgdorferi* have problems of specificity, sensitivity, and reproducibility.[3,4] In the Pacific Northwest, Lyme disease is clearly a rare cause of uveitis. Therefore, using a Bayesian analysis,[5] a positive serologic test for Lyme disease is likely to represent a false-positive result, even if one assumes a high sensitivity and specificity for the ELISA. Our data do not support the routine testing of uveitis patients for Lyme disease. In patients with uveitis, we currently reserve serologic testing for Lyme disease for those patients who have additional symptoms such as cranial neuropathy or arthritis, which may suggest this diagnosis.

References

1. Aaberg, T. M.: The expanding ophthalmologic spectrum of Lyme disease. Am. J. Ophthalmol. 107:77, 1989.

2. Craft, J. E., Grodzicki, R. L., and Steere, A. C.: Antibody response in Lyme disease. Evaluation of diagnostic tests. J. Infect. Dis. 149:789, 1984.

3. Rahn, D. W., and Malawista, S. E.: Lyme disease. Recommendations for diagnosis and treatment. Ann. Intern. Med. 114:472, 1991.

4. Luger, S. W., and Krauss, E.: Serologic tests for Lyme disease. Arch. Intern. Med. 150:761, 1990.

5. Rosenbaum, J. T., and Wernick, R.: The utility of routine screening of patients with uveitis for systemic lupus and tuberculosis. A Bayesian analysis. Arch. Ophthalmol. 108:1291, 1990.

Asymmetric Pigmentary Dispersion Syndrome Mimicking Horner's Syndrome

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The combination of anisocoria and iris heterochromia with the lighter iris on the side of the smaller pupil suggests Horner's syndrome.[1] We treated a patient with this clinical entity who had asymmetric pigmentary dispersion syndrome but did not have Horner's syndrome.

A 41-year-old man came for a routine eye examination. Visual acuity was 20/20 in each eye with a correction of R.E.: −1.75 sph. and L.E.: −1.50 sph. There was iris heterochromia with the lighter iris in the right eye (Fig. 1). The right pupil was visibly smaller than the left (Fig. 1). There was a mild brow ptosis on the right but no true blepharoptosis. Pupillometric studies showed no signs of Horner's syndrome (Fig. 2). No relative afferent pupillary defect was detected. Slit-lamp examination disclosed bilateral Krukenberg spindles, more marked on the left. Iris transillumination defects were not-

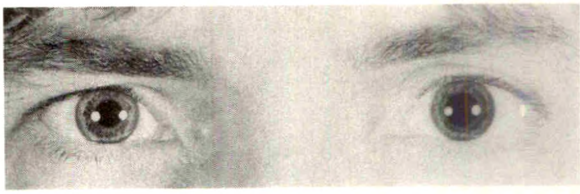

Fig. 1 (Haynes and associates). Photograph of the irides showing iris heterochromia with the lighter iris in the right eye. The right pupil is smaller than the left.

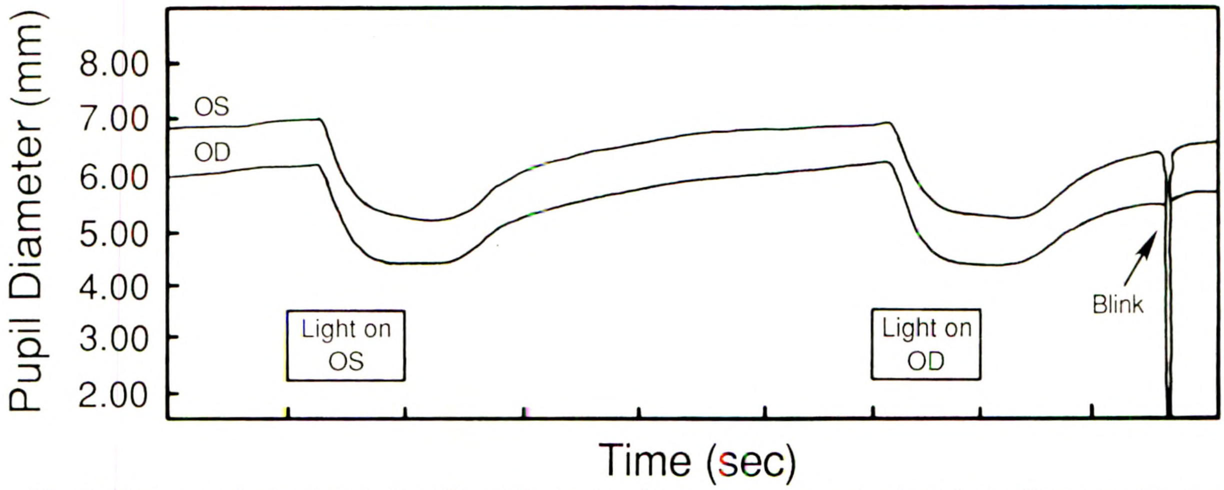

Fig. 2 (Haynes and associates). Pupillometric tracing from a two-channel infrared pupillometer showing anisocoria with the smaller pupil on the right. The anisocoria averaged 0.77 mm in darkness and increased slightly to 0.89 mm in response to a light stimulus of 1-second duration (12 stimulus-response measurements, S.D. = 0.05 mm, $P < .01$, paired *t*-test). There was no dilation lag of the smaller pupil when the light stimulus was turned off. OD indicates right eye; OS, left eye.

ed in both eyes but there were many more in the left eye (the eye with the larger pupil). Pigment granules were present on the iris surface in both eyes but there were far more in the left eye, giving that iris a darker color. Intraocular pressures were R.E.: 26 mm Hg and L.E.: 38 mm Hg. Visual fields were normal. There was slight asymmetry of optic disk cupping with a cup-disk ratio of 0.2 on the right and 0.3 on the left.

Pigmentary dispersion syndrome and pigmentary glaucoma are almost always bilateral conditions. However, a significant number of patients have asymmetric clinical findings. In his review of these conditions, Sugar[2] reported four cases in which the presence of pigment deposition on the iris surface was sufficiently asymmetric to cause the appearance of heterochromia. Feibel and Perlmutter[3] recently reported four cases of anisocoria in patients with asymmetric pigmentary dispersion syndrome, all of whom had a larger pupil in the eye with more iris transillumination defects. These patients did not appear to have Horner's syndrome.

Krebs and associates[4] described a patient with Horner's syndrome and asymmetric pigmentary dispersion syndrome. They hypothesized that the relative miosis on the side of the Horner's syndrome resulted in less iris-zonule contact and therefore less pigment dispersion in that eye. Our patient had clinical signs suggestive of Horner's syndrome. However, the anisocoria seen in our patient did not increase in darkness and there was no dilation lag of the smaller pupil when the light stimulus was turned off. These findings are not consistent with a sympathetic defect as the cause of the anisocoria.

References

1. Miller, N. R.: Disorders of pupillary function, accommodation, and lacrimation. In Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4. Baltimore, Williams & Wilkins, 1985, p. 503.
2. Sugar, H. S.: Pigmentary glaucoma. A twenty-five year review. Am. J. Ophthalmol. 62:499, 1966.
3. Feibel, R. M., and Perlmutter, J. C.: Anisocoria in the pigmentary dispersion syndrome. Am. J. Ophthalmol. 110:657, 1990.
4. Krebs, D. B., Colquhoun, J., Ritch, R., and Liebmann, J. M.: Asymmetric pigment dispersion syndrome in a patient with unilateral Horner's syndrome. Am. J. Ophthalmol. 108:737, 1989.

Acute Conjunctivokeratouveitis Caused By Latex From the Pencil Tree

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The pencil tree, *Euphorbia tirucalli,* is an ornamental garden plant with green juicy stalks, which has been increasingly cultivated in recent years.[1] Many species of *Euphorbia* contain a latex that, if accidentally squirted into the human eye, causes keratoconjunctivitis or uveitis of varying degrees of severity.[2,3] Such reactions were experimentally produced also by the pencil tree latex in rabbit and dog eyes.[4] We treated two patients who had eye injuries caused by the pencil tree latex.

Case 1

A 39-year-old man felt latex squirt into his left eye while working in the garden. He had an intense burning sensation despite copious washout with water. A few hours later, ophthalmic examination of the left eye disclosed visual acuity of 20/40, eyelid edema, conjunctival chemosis, punctate corneal erosion, stromal edema (corneal thickness, 0.8 mm), and central corneal haziness. Intraocular pressure, the anterior chamber and fundus were normal. Despite patching of the eye with 5% chloramphenicol ophthalmic ointment, his visual acuity decreased the next day to 20/400. Examination showed a total corneal erosion and a white streak-like infiltration extending into the midstroma from the 2:00 to the 12:00 o'clock meridian with moderate anterior chamber flare and cells (Fig. 1). Dexamethasone sodium phosphate and neomycin sulfate eyedrops, every six hours, and 1% cyclopentolate eyedrops, every eight hours, were added to his treatment. Cultures taken from the conjunctival sac for microbes were negative. Within 48 hours his visual acuity improved to 20/40, the stromal infiltrate began to fade, reepithelization of the cornea progressed and the anterior chamber reaction markedly diminished. The specular endothelial cell count was within normal limits. After four days visual acuity returned to 20/20 and the anterior segment cleared completely.

Case 2

A 42-year-old man had severe burning and pain in his left eye while pruning a pencil tree. Despite prolonged and copious rinsing with water, he had no relief. Two hours later he had conjunctival injection, punctate epithelial corneal erosions, and visual acuity of 20/20. The anterior chamber, intraocular pressure, and fundus were normal. Initial treatment consisted of patching the eye with 5% chloramphenicol ointment. Two days later his condition worsened, and visual acuity was hand movements from 1 m. Ophthalmic examination showed marked ciliary injection, punctate erosions, Descemet's folds, epithelial bullae, and corneal thickening (0.9 mm). Severe anterior chamber flare and cells and a 2.6-mm hypopyon occurred (Fig. 2). Microbial cultures taken from the conjunctival sac were negative. Dexamethasone sodium phosphate and neomycin sulfate eyedrops, every two hours, and cyclopentolate 1% eyedrops, every eight hours, were instilled; 3 mg of betamethasone disodium phosphate and betamethasone acetate was injected subconjunctivally. Three days later there was no hypopyon and the anterior chamber was clear. One week later endothelial cell count was normal and visual acuity returned to 20/20.

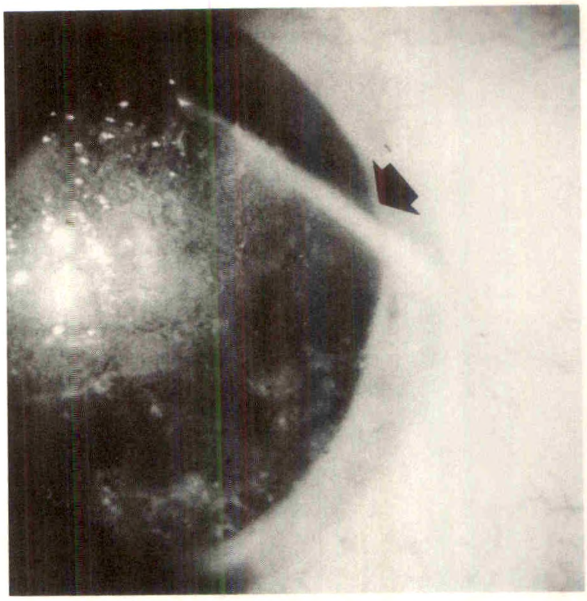

Fig. 1 (Desatnik and associates). Case 1. Corneal edema, diffuse punctate erosions, and a streak-like stromal infiltrate (arrow).

The active ingredients of *E. tirucalli* latex have been identified as irritant ingenane and tagliane type diterpene esters derived from unsaturated aliphatic acids and acetic acid and the polyfunctional diterpene parent alcohols 4-deoxypharbol, pharbol and ingenol, respectively.[5] The accidental instillation of the plant latex into the eye causes keratoconjunctivitis or anterior uveitis despite immediate and copious rinsing with water and continued irrigation in the

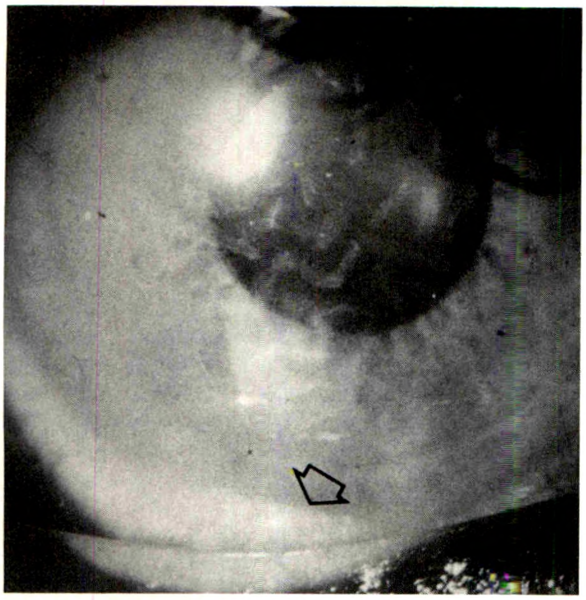

Fig. 2 (Desatnik and associates). Case 2. Corneal edema, Descemet's folds, and hypopyon (arrow).

emergency clinic. It appears that, depending on the amount of latex squirted into the eye, ocular damage including punctate keratitis, stromal infiltrate (Case 1), and marked anterior uveitis with hypopyon (Case 2) may occur. Because of the sterile cultures, presumably these reactions were chemically induced by the irritant effect of the active ingredients of the latex. Good clinical response to intensive treatment with local corticosteroids and antibiotics resulted in short-term improvement with a full functional and structural recovery. Moreover, it seems prudent to advise the use of a tight-fitting mask or goggles while working with pencil tree ornamental plants.

References

1. Waisel, Y., and Cohen, S.: Poison plants in Israel. Petach Tikvah, Ministry of Environmental Ecology in Israel, 1977, p. 32.

2. Hartmann, K.: Augenschadigungen durch den saft der Euphorbia peplus. Klin. Monatsbl. Augenheilkd. 104:324, 1940.

3. Geidel, K.: Klinische Beobachtung und tierexperimentalle undersuchungen uber die Wirkung von saft der *Euphorbia lathyris* (Springwolfsmilch) am. Klin. Monatsbl. Augenheilkd. 141:374, 1962.

4. Crowder, J. I., and Sexton, R. R.: Keratoconjunctivitis resulting from the sap of candelabra cactus and the pencil tree. Arch. Ophthalmol. 72:476, 1964.

5. Furstenberger, G., and Hecker, E.: On the active principles of the spurge family (Euphorbiaceae). The skin irritant and tumor promoting diterpene esters of *Euphorbia tirucalli L* originating from South Africa. Z. Naturforsch. [C] 40:631, 1985.

Concurrent Chlamydial and *Acanthamoeba* Keratoconjunctivitis

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An 18-year-old man who wore soft contact lenses developed redness and irritation in his left eye. His father, a pharmacist, empirically initiated a regimen of topical gentamicin sulfate eyedrops. An ophthalmologist began treatment with fluorometholone, sulfacetamide sodium ophthalmic suspension, and trimethoprim sulfate/polymyxin B sulfate ophthalmic solution. The patient's symptoms rapidly progressed to pain, photophobia, and decreased vision over the next three days and he was referred for consultation.

The patient used a cold disinfection system and commercial saline to clean his contact lenses. He was sexually active with multiple female partners.

At examination, clinical findings were confined to the left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/200. Preauricular adenopathy was present on the left. Slit-lamp examination of the left eye disclosed marked injection of conjunctival and episcleral vessels, moderate tarsal follicles, and patchy nummular opacification of the anterior corneal stroma and basal epithelium. The corneal epithelium was intact and moderate anterior chamber reaction was also present (Fig. 1). Bacterial and fungal cultures were negative but a direct fluorescein-

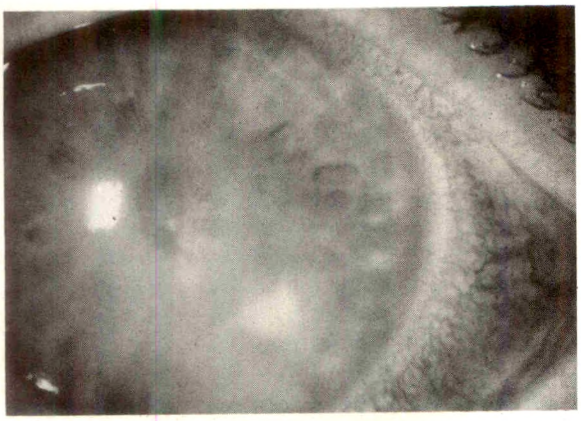

Fig. 1 (Reddy and associates). Paracentral and midperipheral nummular corneal opacification associated with moderate anterior uveitis and conjunctival injection.

conjugated antibody test for chlamydia was unequivocally positive. A Giemsa stain of the conjunctival scrapings disclosed multiple intracytoplasmic inclusion bodies consistent with the diagnosis of chlamydial keratoconjunctivitis (Fig. 2). A regimen of orally administered doxycycline and topical tetracycline was started.

The patient's clinical course waxed and waned during the next two weeks with respect to the keratitis, and the anterior uveitis persisted. A repeat culture, direct fluorescein-conjugated antibody test, and polymerase chain reaction for chlamydia were all negative, indicating resolution of the chlamydial infection. Cultures for bacteria, fungi, and herpes simplex virus were also negative. *Acanthamoeba* species was isolated from a corneal scraping plated onto nonnutrient agar enriched with *Escherichia coli*. Intensive topical therapy consisting of neomycin sulfate, clotrimazole, and propamidine was initiated, which resulted in marked resolution of active keratitis and uveitis, residual stromal scarring in a ring pattern, and visual acuity of counting fingers. The patient underwent an uncomplicated penetrating keratoplasty two months after initial manifestation. Because the patient developed peripheral corneal neovascularization, the decision was made to perform the corneal transplant. Histopathologic study of the corneal button disclosed neither trophozoites nor cysts. Five months after surgery, the patient's visual acuity with spectacles was 20/25, with a clear and compact penetrating keratoplasty and white, uninflamed eye.

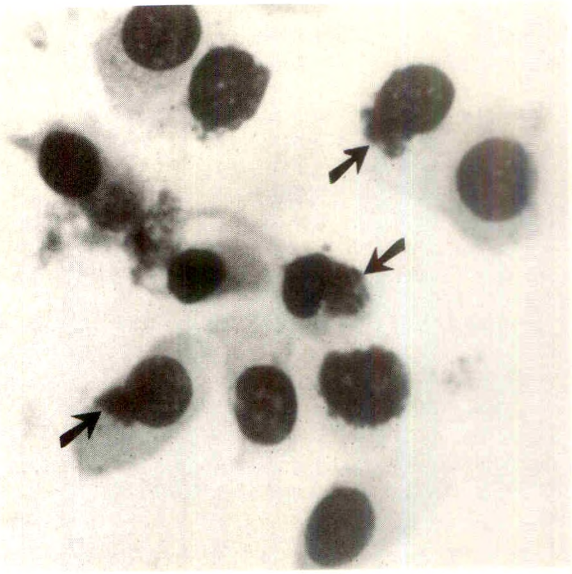

Fig. 2 (Reddy and associates). Giemsa stain demonstrates intracytoplasmic basophilic inclusion bodies in conjunctival epithelial cells (arrows).

Bacterial, fungal, and viral infections occurring concurrently with *Acanthamoeba* keratitis have been reported previously.[1,2] It is not known what role, if any, these organisms had in the pathogenesis of the amebic keratitis. Experimental evidence suggests, however, that previous bacterial and viral infection may potentiate *Acanthamoeba* infection.[3] Bacteria and damaged host cells may serve as the initial source of nutrition for the ameba at the time of inoculation and enhance its infectivity. Our case suggests that a similar mechanism may apply also to chlamydia and that further laboratory studies of potential synergy between these microbial agents may prove useful.

The role and timing of penetrating keratoplasty in *Acanthamoeba* keratitis have been the subject of considerable debate. Penetrating keratoplasty has a higher success rate if performed on an eye before the organism has disseminated throughout the cornea or before extensive damage to the tissues has occurred; however, recurrence of infection after the initial operation appears to be more common if the transplant is performed within four months of the onset of infection.[4] In our case, early keratoplasty was favored because of the dramatic response to intensive medical therapy and the development of peripheral corneal neovascularization, which if allowed to progress, would have increased the risk of graft rejection.

References

1. Mannis, M. J., Tamaru, R., Roth, A. M., Burns, M., and Thirkill, C.: *Acanthamoeba* sclerokeratitis. Arch. Ophthalmol. 104:1313, 1986.
2. Moore, M. B., McCulley, J. P., Luckenbach, M. D., Gelender, H., Newton, C., McDonald, M. B., and Visvesvara, G. S.: *Acanthamoeba* keratitis associated with soft contact lenses. Am. J. Ophthalmol. 100:396, 1985.
3. Jones, D. B., Visvesvara, G. S., and Robinson, N. M.: *Acanthamoeba polyphaga* keratitis and *Acanthamoeba* uveitis associated with fatal meningoencephalitis. Trans. Ophthalmol. Soc. U.K. 95:221, 1975.
4. Auran, J. D., Starr, M. B., and Jakobiec, F.: *Acanthamoeba* keratitis. A review of the literature. Cornea 6:2, 1987.

Bilateral Herpes Simplex Keratitis in a Patient With Graft-vs-Host Disease

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Herpes simplex keratitis is characteristically unilateral, with a reported bilateral incidence ranging from 1% to 10%.[1] We treated a patient with culture-proven bilateral herpetic keratitis who was suffering from graft-vs-host disease.

Chronic myelogenous leukemia had been diagnosed in a 23-year-old woman, and she had undergone three bone marrow transplants in 1988, with recurrent episodes of graft-vs-host disease. She suffered from keratoconjunctivitis sicca, for which she had undergone bilateral lower eyelid thermal punctal occlusions, and had experienced several episodes of herpetic eye disease in the left eye. At the time of referral, she was on a regimen of homatropine 5%, one drop at bedtime in each eye; gentamicin, one drop every two hours in each eye; and sodium sulfacetamide 10% with prednisolone acetate 0.2%, one drop every 12 hours in each eye. She was also taking prednisone, 20 mg orally every other day, and cyclosporine, 70 mg once a day.

Best-corrected visual acuity was R.E.: 20/40 and L.E.: 20/25. Slit-lamp examination disclosed bilateral dendritic keratitis with diffuse punctate keratitis and recanalized inferior puncta. Scrapings for herpes simplex culture were obtained from each eye. Her eyedrops were discontinued, the inferior puncta were recauterized, and trifluridine, one drop every two hours in each eye, and polymyxin B-bacitracin ointment, four times a day in both eyes, were prescribed. The herpes cultures (monoclonal-antibody staining method) were positive for each eye, and her dendritic keratitis completely resolved after ten days of treatment.

Although rare, bilateral herpetic keratitis has been diagnosed in young patients with atopy,[2] and it has been reported in patients with measles[3] and patients with altered immune systems. It commonly has a higher proportion of subsequent complications, as compared to unilateral herpetic eye disease.[4]

Graft-vs host disease is a major complication that occurs after an allogenic bone marrow transplant and results from the reaction of transplanted, immunocompetent cells against the host. Graft-vs-host disease occurs in 50% to 70% of patients after an allogenic bone marrow transplant. The most frequent ocular manifestations include keratoconjunctivitis sicca, cicatricial lagophthalmos, and sterile conjunctivitis and uveitis.[5]

Our case suggests that herpes keratitis should be considered in the differential diagnosis of bilateral keratitis in a patient with altered host susceptibility. Virologic evaluation may play an important role in determining the origin of the underlying keratitis and defining the appropriate treatment for the patient.

References

1. Ostler, H. B.: Herpes simplex. The primary infection. Surv. Ophthalmol. 21:91, 1976.
2. Easty, D., Entwistle, C., Funk, A., and Wichter, J.: Herpes simplex keratitis and keratoconus in the atopic patient. A clinical and immunological study. Trans. Ophthalmol. Soc. U.K. 95:267, 1975.
3. Sachs, U., and Marcus, M.: Bilateral herpetic keratitis during measles. Am. J. Ophthalmol. 91:796, 1981.
4. Wilhilmus, K. R., Falcon, M. G., and Jones, B. R.: Bilateral herpetic keratitis. Br. J. Ophthalmol. 65:385, 1981.

5. Franklin, R. M., Kenyon, K. R., Tutschka, P. J., Saral, R., Green, W. R., and Santos, G. W.: Ocular manifestations of graft-vs-host disease. Ophthalmology 90:4, 1983.

Canalicular Obliteration From Toxic Epidermal Necrolysis

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Toxic epidermal necrolysis is a severe, exfoliative, full-thickness epidermal slough involving the skin and mucosa.[1] Ophthalmic manifestations include pseudomembranous conjunctivitis, keratoconjunctivitis sicca, conjunctival scarring with resultant symblepharon, conjunctival cyst, corneal ulcer, corneal perforation, corneal vascularization, eyelid deformity, trichiasis, punctal obliteration, cicatricial entropion, metaplasia of meibomian glands, and stenosis of lacrimal gland ductules.[2] We encountered a case of canalicular obliteration.

A 25-year-old, previously healthy woman developed itchy eyes, a sore throat, and bleeding of the gums. Two days later, she was admitted to Presbyterian Medical Center because of a follicular conjunctivitis, mucosal blisters in the mouth, and a fever of 103 F. The patient developed tender blisters on her arms and legs, which progressed over two days, coalescing to involve the entire skin surface. A skin biopsy specimen showed toxic epidermal necrolysis. The patient was treated with intravenous nafcillin, gentamicin, and clindamycin. One month later, the patient was seen at the Scheie Eye Institute because she had developed bilateral constant epiphora. Examination disclosed cutaneous scarring and hypopigmentation of the skin (Fig. 1) as well as scarring of the punctum at all four lacrimal papillae (Fig. 2). The patient underwent lacrimal exploratory surgery. Punctoplasty and probing disclosed obliteration of all four canaliculi. Bilateral conjunctivodacryocystorhinostomies were performed, which function well after seven years.

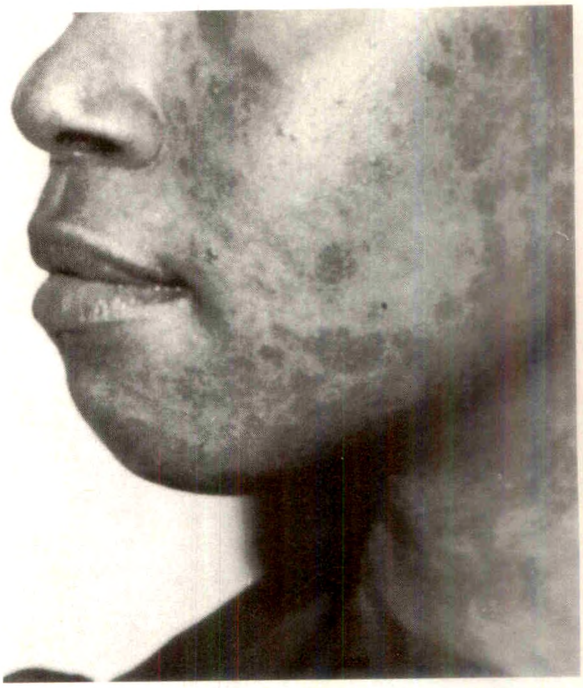
Fig. 1 (Leahey and associates). Skin on the face shows areas of scarring and hypopigmentation.

Toxic epidermal necrolysis has a mortality of 25% to 100%, because of associated sepsis and metabolic abnormalities that occur secondary to evaporation across the denuded skin surface.[1] Treatment involves massive fluid and electrolyte replacement, and antibiotics if sepsis develops. Treatment with systemic corticosteroids is of controversial benefit.[1]

On the basis of its occurrence in Stevens-Johnson syndrome, a condition with closely allied ocular findings, canalicular obliteration can be expected in toxic epidermal necrolysis.[2,3] Treatment of canalicular obliteration involves canalicular exploration with intubation if canalicular remnants remain. If they do not, then conjunctivodacryocystorhinostomy with insertion of Jones tubes may be required.[4]

Five to 9% of toxic epidermal necrolysis survivors have poor visual function from dry-eye to symblepharon, corneal scarring, and lacrimal duct obstruction.[1] Despite the destruction of tear-producing glands that occurs after toxic epidermal necrolysis, our case illustrates that

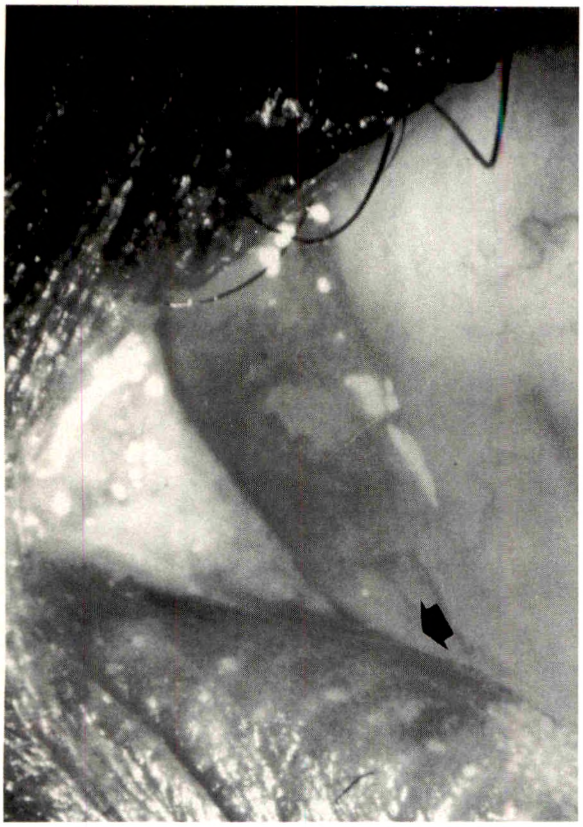

Fig. 2 (Leahey and associates). Scarring of the punctum (arrow) of the left lower eyelid.

overflow tearing may also occur in this syndrome.

References

1. Heimbach, D. M., Engrav, L. H., Marvin, J. A., Harnar, T. J., and Grube, B. J.: Toxic epidermal necrolysis. A step forward in treatment. JAMA 257:16, 1987.

2. Revuz, J., Penso, D., Roujeau, J., Guillaume, J., Payne, C. R., Wechsler, J., and Touraine, R.: Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. Arch. Dermatol. 123:1160, 1987.

3. Howard, G. M.: The Steven's Johnson syndrome. Ocular prognosis and treatment. Am. J. Ophthalmol. 55:5, 1963.

4. ———: Lacrimal system. In Katowitz, J. A. (ed.): Orbit, Eyelids and Lacrimal System. Basic and Clinical Science Course, Sec. 9. San Francisco, American Academy of Ophthalmology, 1990–1991, pp. 207–236.

Metastatic Carcinoid Tumor Diagnosis from a Caruncular Mass

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Carcinoid tumors metastatic to the eye and orbit are rare, and the few reported lesions within the ocular region typically have been in the choroid or orbit.[1] We studied a case of carcinoid tumor, which was diagnosed initially from a lesion metastatic to the caruncle.

A 70-year-old woman had a history of a bloody discharge from her left eye for several months. She had developed a mass in the left caruncle three weeks before being seen by an ophthalmologist. Physical examination disclosed a nodular, erythematous mass of the left caruncle (Fig. 1). The mass was excised and submitted for histopathologic examination.

Histologically, the specimen consisted of caruncular tissue infiltrated by a neoplastic process. This process assumed an organized pattern at multiple sites, with some areas suggestive of trabecular organization and other areas exhibiting some formations resembling a rosette (Fig. 2). There were oval to round neoplastic cells, each containing scanty cytoplasm, a round nucleus, and a tiny nucleolus. Most of the cells contained a lightly basophilic nucleus, but there was also a population of cells with darkly basophilic nuclei. These dark cells were typically located around the periphery of the lesion.

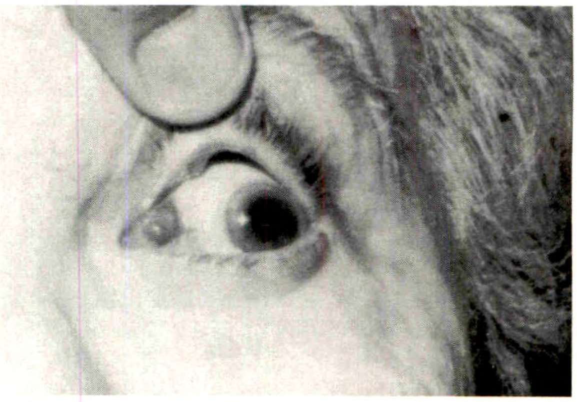

Fig. 1 (Gritz and Rao). Clinical photograph of lesion of left caruncle.

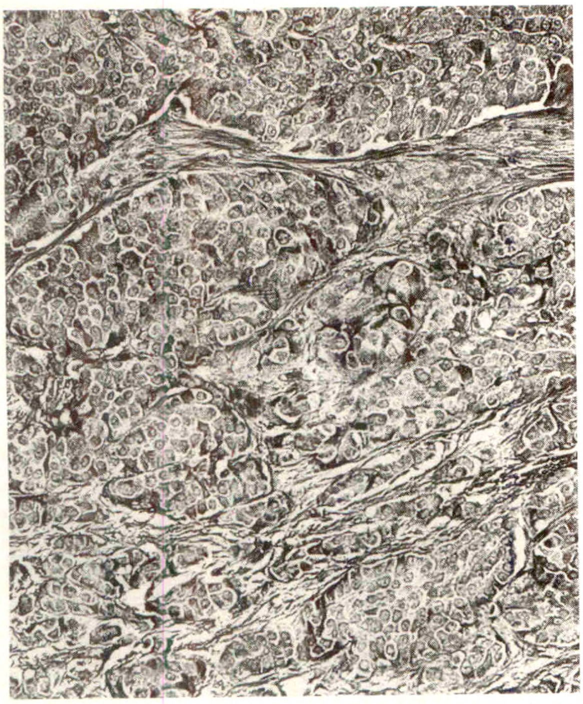

Fig. 2 (Gritz and Rao). Photomicrograph of the lesion, showing the trabecular pattern of cells (hematoxylin and eosin, × 140).

There was no mitotic activity in the sections studied. Differential diagnosis at this point included a metastatic carcinoid tumor or a low-grade melanoma. Special stains were performed. Gremilius, an argyrophilic stain, was positive. Immunohistochemical stains for neuron-specific enolase, chromogranin, and synaptophysin were also positive. The final diagnosis was metastatic carcinoid tumor of the caruncle. The patient was referred to an oncologist for further diagnostic examination.

On further questioning, the patient complained of generalized itching and flushing, but denied diarrhea, wheezing, and abdominal pain. Physical examination disclosed no physical signs of carcinoid syndrome. Serum serotonin level was 1,435 ng/ml (normal adult woman, 120 to 326 ng/ml; patients with carcinoid, 940 to 3,500 ng/ml). Twenty-four hour urine collection contained 15 mg of 5-hydroxyindoleacetic acid (normal < 6 mg/24 hours). Computed tomography of the abdomen and pelvis showed faint low-density lesions within the liver, ranging in size from 10 to 20 mm. Subsequent hepatic sonogram disclosed two echogenic lesions within the right lobe of the liver; these lesions were believed to be metastatic lesions from a primary tumor that was most likely located in the small intestine.

Carcinoid is a generic term referring to neoplasms originating from enterochromaffin cells.[2] They commonly occur in the midgut, particularly the appendix, but may also occur at other gastrointestinal sites or even outside the gastrointestinal tract. Metastatic dissemination is rare from primary lesions in the appendix and rectum, but is relatively common from carcinoid tumors of ileal, gastric, and colonic origin. Cases of ocular metastasis are rare, and those reported were from primary lesions of the ileum and bronchus, when a primary site was found.[1,3] Most ocular metastases have been to the orbit and choroid, with an even rarer metastasis to the iris.[1,4]

Carcinoid syndrome is diagnosed when a patient has any of the following symptoms: cutaneous flushing, telangiectasia, wheezing, abdominal pain, edema, and a rash resembling pellagra. Increased serum serotonin levels and increased urinary levels of 5-hydroxyindoleacetic acid, one of the metabolic metabolites of serotonin, are associated with the carcinoid syndrome. Although few solitary carcinoid tumors of the midgut produce carcinoid syndrome, it is common when these same tumors metastasize.[5]

Treatment of carcinoid syndrome has two objectives: reducing tumor mass by surgical or chemotherapeutic methods and relief of humorally mediated symptoms. The patient described here is presently being treated with cyproheptadine hydrochloride, an antihistaminic and antiserotonergic agent useful in treating the itching and flushing, and cimetidine, which acts as a histamine H2 antagonist, thereby inhibiting the excess secretion of gastric acid caused by histamine. She has not developed any further symptoms; serum serotonin level has since decreased to 503 ng/ml.

References

1. Riddle, P. J., Font, R. L., and Zimmerman, L. E.: Carcinoid tumors of the eye and orbit. A clinicopathologic study of 15 cases, with histochemical and electron microscopic observations. Hum. Pathol. 13:495, 1982.
2. Cotran, R. S., Kumar, V., and Robbins, S. L.: Pathologic Basis of Disease, ed. 4. Philadelphia, W. B. Saunders, 1989, pp. 802; 803; 872–875.
3. Shetlar, D. A., Font, R. L., Ordôñez, N., El-Naggar, A., and Boniuk, M.: A clinicopathologic study of three carcinoid tumors metastatic to the orbit. Immunohistochemical, ultrastructural, and

DNA flow cytometric studies. Ophthalmology 97:257, 1990.

4. Archer, D. B., and Gardiner, T. A.: An ultrastructural study of carcinoid tumor of the iris. Am. J. Ophthalmol. 94:357, 1982.

5. Oates, J. A., and Roberts, L. J. H.: Carcinoid syndrome. In Braunwald, E., Issilbacher, K. J., Petersdorf, R. G., Wilson, J. D., Martin, J. B., and Fauci, A. S. (eds.): Harrison's Principles of Internal Medicine, ed. 11. New York, Magraw Hill, 1987, pp. 1585–1588.

Immunohistochemistry Findings in Primary Intraocular Lymphoma

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Primary intraocular lymphoma is a rare, usually bilateral (in 75% to 80% of cases) neoplasm with a predilection for central nervous system involvement.[1] Over 100 cases have been reported since 1951.[2] However, the immunohistochemistry of this tumor has not been well delineated.

A 48-year-old woman had a five-month history of persistent posterior vitreitis. She had vitreous floaters and blurred vision and was treated with 60 mg per day of prednisone, administered orally. Despite some initial improvement, the uveitis again worsened and her visual acuity deteriorated to R.E.: 20/60 and L.E.: hand motions. Computed tomography scans of the brain and the orbits, as well as results of the neurologic examination, including cerebrospinal fluid, were normal. Because of optic nerve edema in her left eye, an optic nerve sheath fenestration was performed with a diagnostic vitrectomy, which disclosed reactive

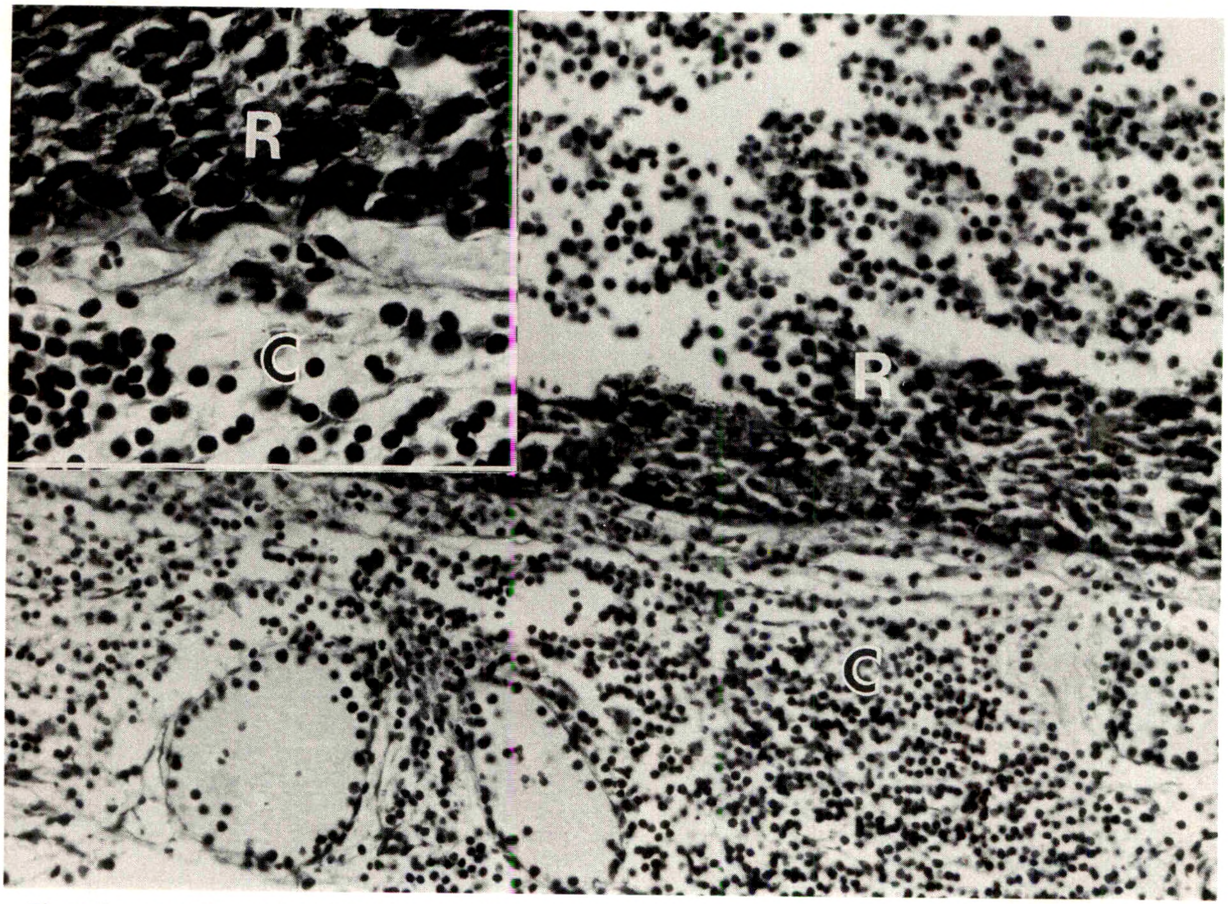

Fig. 1 (Lopez and associates). Tumor cells located above Bruch's membrane and infiltrating lymphocytic cells located in the choroid. R indicates retina; C, choroid (hematoxylin-eosin, × 200; inset, × 400).

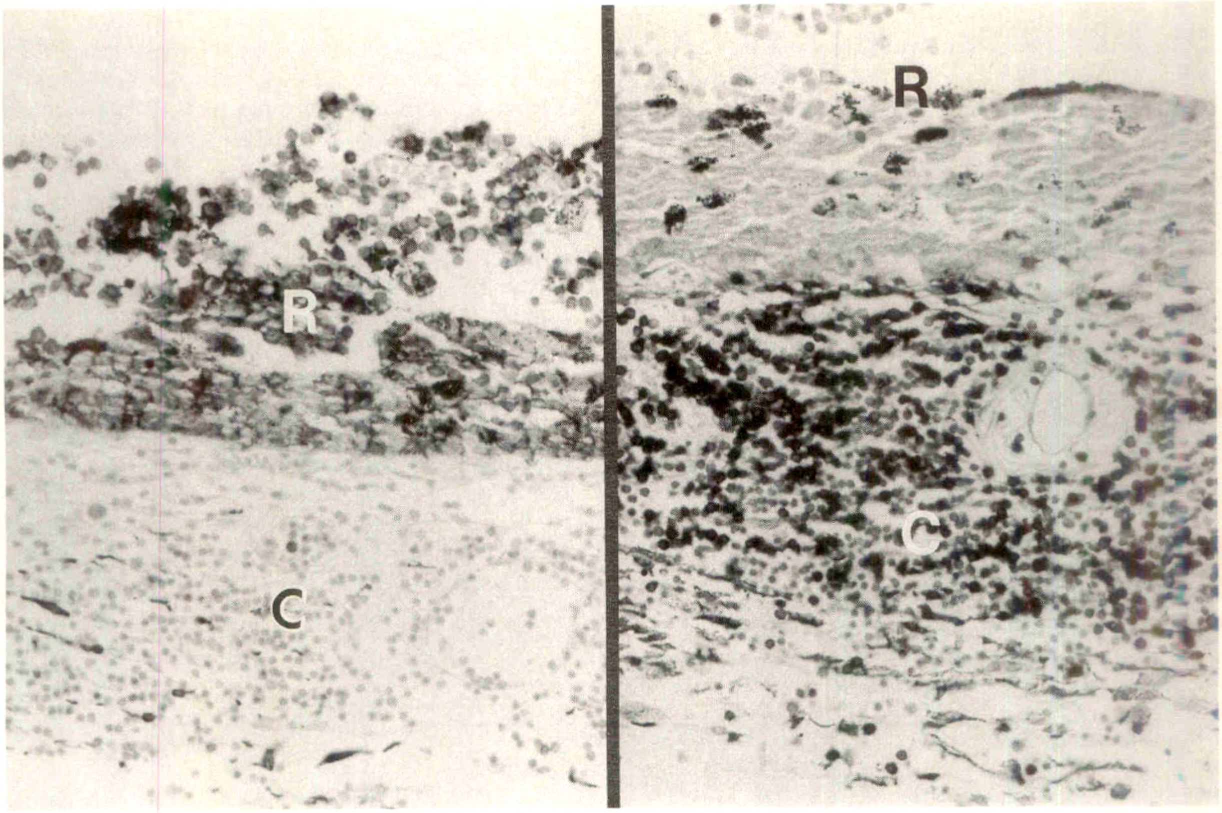

Fig. 2 (Lopez and associates). Left, Retinal tumor cells stained positively for the B-cell marker, L26. Right, Infiltrating lymphocytic cells in the choroid stained for the T-cell marker, UCHL1. R indicates retina; C, choroid (avidin-biotin-peroxidase, × 200).

lymphocytes. Cellular marker studies, however, were not performed.

When the patient was referred to the National Eye Institute, her visual acuity was R.E.: 20/100 and L.E.: light perception. Ocular examination disclosed yellow-white retinal infiltrates interspersed with hemorrhages in both eyes. The vitreous had severe cells, some of which aggregated into clumps and sheets. Examination of cerebrospinal fluid failed to disclose any abnormal cells on two occasions. A second vitrectomy performed on the left eye was not diagnostic. Repeat computed tomography of the brain, however, showed thickening of the left posterior globe and enhanced areas in the right posterior parietal and occipital lobes.

Two weeks later, visual acuity decreased further to R.E.: 20/200 and L.E.: no light perception. Further tests disclosed no other foci. Enucleation of her left eye was performed to establish the nature of her disease.

Microscopic examination of the enucleated globe disclosed multiple foci of large lymphocytic cells between the retinal pigment epithelium and Bruch's membrane, with the largest foci located adjacent to the optic nerve head. Numerous lymphocytic cells were also present in the choroid, particularly beneath the retinal lymphoid tumor cells (Fig. 1). Immunohistochemical staining showed that the majority of these retinal lymphoid tumor cells stained with B-cell (CD19, 20, 22) and kappa light chain markers, with occasional cells staining for T-cell (CD3) and macrophage (CD11c) markers (Fig. 2, left). In contrast, the majority of the lymphoid cells in the choroid stained for T-cell (CD3) markers, with a ratio of 2:1 between T-helper/inducer (CD4) and T-cytotoxic/suppressor (CD8) cells. Most of the CD8 cells were located adjacent to Bruch's membrane, whereas the CD4 cells were evenly distributed in the choroid (Fig. 2, right). A few macrophages were found surrounding the choroidal infiltrates of T cells.

Our finding of a sharp demarcation between the B lymphoid tumor cells in the retina and infiltrating T lymphocytes in the choroid is interesting. The nature of this lymphoid cell compartmentalization is unclear. The T cells may be involved in preventing tumor exit into the choroid; that could account for the absence of choroidal involvement in intraocular large B cell lymphomas.[3] Conversely, the lack of infiltrating T cells anterior to Bruch's membrane may allow for the rapid growth and invasion of B cell lymphomas into the retina and vitreous. Other factors, such as the antigenicity of the tumor and the ability of the host to mount an immune response should also be taken into account.[4] Whether this type of immune response actually promotes or inhibits tumor B-cell proliferation remains an area of speculation.

References

1. Char, D. H., Ljung, B. M., Miller, T., and Philips, T.: Primary intraocular lymphoma (ocular reticulum cell sarcoma) diagnosis and management. Ophthalmology 95:625, 1988.
2. Lewis, H., and Schachat, A.P.: Non-Hodgkin's ("reticulum cell") lymphoma. In Ryan S. J., and Ogden, T. E. (eds.): Retina, Vol. 1. Basic Science and Inherited Retinal Disease. St. Louis, C. V. Mosby, 1989, pp. 795–802.
3. Klingele, T. G., and Hogan, M. J.: Ocular reticulum cell sarcoma. Am. J. Ophthalmol. 79:39, 1975.
4. Reif, A. E.: Some key problems for success of classic immunotherapy. In Reif, A. E., and Mitchell, M. S. (eds.): Immunity to Cancer. Orlando, FL, Academic Press, 1985, pp. 3–16.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

The Elastic Properties of the Lens Capsule in Capsulorhexis

EDITOR:

In the article, "The elastic properties of the lens capsule in capsulorhexis," by E. I. Assia, D. J. Apple, J. C. Tsai, and E. S. Lim (Am. J. Ophthalmol. 111:628, May 1991), the following technique to demonstrate elasticity of the capsule was described. Circular capsulorhexis openings were stretched in postmortem eyes by using modified calipers until the margins were torn. In this way a circular opening was converted to a linear opening.

If we use simple mathematical concepts, the diameter of a circle is equal to twice its radius. If we stretch this same circular structure to a linear one, as was described in the article, the length of that opening would be one half of its circumference, or πr. We can thus determine the ratio of the stretched opening (πr) to the diameter ($2r$). Mathematically this is 1.57 (3.14159/2). The apparent 57% stretch of the capsule when converting from a circular to a linear opening has nothing to do with elasticity, but rather only proves a geometric construct. What the authors have shown is that in postmortem eyes the capsule is able to withstand this deformation.

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JOEL ROSEN, M.D., F.R.C.S.(C)
Montreal, Quebec, Canada

Reply

EDITOR:

We believe Drs. Budning and Rosen have misinterpreted our experimental results; this is a misinterpretation that, if uncorrected, detracts from what is known to be a clinically useful advantage of the continuous, circular or curvilinear capsulorhexis technique. An important feature of this technique is that a capsulorhexis opening can not only be deformed during surgical manipulation, but can also be stretched and widened a finite amount before formation of radial tears of the anterior capsule. The experimental measurements documented in our article clearly show that there is not only a change in diameter of the capsular opening because of geometric deformation, as Drs. Budning and Rosen noted, but also an additional capsule stretching component that they have apparently overlooked.

Their calculation, namely that a change in shape of a circular capsulorhexis to a linear opening (without a change in circumference) would increase the diameter by a value of $\pi/2$ or a factor of 1.57, is correct. According to this calculation, a simple conversion from a circular to a linear opening, without an elastic or stretch component, indeed provides a 57% increase in diameter.

The discrepancy occurs because Drs. Budning and Rosen used diameters in their calculations instead of circumferences, as was done in our study. They compared capsulectomy diameter (Dc) to the diameter at rupture (Dr). In our study, if we had done this, as Drs. Budning and Rosen suggested, the number we experimentally arrived at would have been 2.3, or 70% greater than the figure they stated. This is because the observed increase was not only the theoretical 1.57 value calculated mathematically and related simply to the geometric deformation, but also includes an added factor of 0.73 (2.3 − 1.57), which indeed represents the stretching ability of the capsule. The theoretical mathematical corrections of Drs. Budning and Rosen are correct, but do not complete the equation. Our measured actual values clearly document an additional stretching component.

In our study, the results are shown as a ratio between the circumference at rupture (Cr) and circumference of the capsulectomy (Cc). If there were no stretch factor, that is, if there were no elasticity, the value of circumference at rupture over circumference of the capsulectomy (Cr/Cc) would be 1.0. Our measured result, however, was 1.6. This reflects a real increase in circumference and an additional stretch of 60% of the capsule. This value of 1.6 has nothing to do with the value of $\pi/2$ or 1.57 noted in the calculation of the diameter; the similarity here is a coincidence.

In clinical terms, a knowledge of this stretch factor is important to determine the size that a capsulectomy may assume during surgical manipulations before capsular tear formation. For example, when a surgeon performs a 4.5-mm continuous, circular capsulorhexis (Figure 1 in the article), according to our data, the capsulectomy will convert to a slit of approximately 10.4 mm, just before rupture. A simple deformation of the orifice, that is, by simply changing the geometric construct without any stretch on the capsule, would have given a length of approximately 7 mm. Therefore, the additional amount of 3.4 mm (10.4 − 7 mm) can only by accounted for by the stretching ability of the capsule.

During clinical removal of lens material, the actual change in geometric shape from a circular opening never proceeds to a complete geometric slit because there is thickness to the crystalline lens. This is shown in Figure 3 of our article. Therefore, there is a "safety zone" of what diameter of capsulectomy can be safely made as compared to the diameter of an inserted intraocular lens or the removed lens material that must pass through the capsular opening (Figure 4).

When manipulated, the diameter of the anterior capsulectomy increases because of two factors: first, a change in configuration from a circle toward a slit-like structure, causing a 57% increase in diameter, clearly representing the change in geometric construct. This is what the authors referred to in their letter. However, to correlate with the experimental measurements, the second factor must be present, namely a stretching of the capsule, which increased the diameter by an additional 60% to 70% (2.3 vs 1.6 mm, using the above-mentioned ratios). Drs. Budning and Rosen have accounted for the mathematical change in configuration, that is, the deformation from a circle to a slit, but apparently overlooked the measurements that show an additional increase in size, which had to be related to a stretching of the capsule.

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Ultrastructural Study of Norrie's Disease

EDITOR:

In the article, "Ultrastructural study of Norrie's disease," by L. B. Enyedi, E. de Juan, Jr., and A. Gaitan (Am. J. Ophthalmol. 111:439, April 1991), the authors described the light microscopic and electron microscopic features of a vitreoretinal biopsy specimen from an infant with Norrie's disease.

The specimens demonstrated signs of poor development of the retinal vascular network.

The authors speculated about the origin of the severe fibrovascular organizations in the anterior vitreous cavity. Like others,[1,2] they suppose that this tissue could be derived from the primary vitreous. Another explanation is that the fibrovascular tissue has a neovascular origin. Some observations support this hypothesis: rapid postnatal progression has been observed in infants with Norrie's disease,[3] which suggests that at least part of the fibrovascular tissue is not a fetal remnant. The observation of the poor vascular supply of the retina in Norrie's disease[4] also points to the possibility of neovascularization caused by retinal ischemia.

The statement by the authors that familial exudative vitreoretinopathy is not associated with an avascular retina should be corrected: the most prominent and characteristic feature of familial exudative vitreoretinopathy is the avascularity of the peripheral retina. The configuration of the vascular network suggests that the latter disease is a disorder of development of the retinal vascular system.[5]

Several diseases associated with infantile or juvenile retinal detachment such as retinopathy of prematurity, familial exudative vitreoretinopathy,[5,6] and incontinentia pigmenti[7] have been recognized as proliferative retinopathies. The vascular proliferations that may complicate these three disorders are secondary to the specific arrest of retinal vascular development.

The study of Enyedi and coworkers has added evidence to the supposition that Norrie's disease is associated with a severe underdevelopment of the retinal vascular system.

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References

1. Warburg, M.: Norrie's Disease. A Congenital Progressive Oculoacoustico-cerebral Degeneration. Copenhagen, Bogtrykkeriet Forum, 1966, p. 40.

2. Apple, D. J., Fishman, G. A., and Goldberg, M. F.: Ocular histopathology of Norrie's disease. Am. J. Ophthalmol. 78:196, 1974.

3. Jacklin, H. N.: Falciform fold, retinal detachment and Norrie's disease. Am. J. Ophthalmol. 90:76, 1980.

4. Fujita, S., Fujiwara, N., and Ohba, N.: Norrie's disease. Report of cases in two Japanese families. Jpn. J. Ophthalmol. 24:22, 1980.

5. Van Nouhuys, C. E.: Dominant exudative vitreoretinopathy and other vascular developmental disorders of the peripheral retina. The Hague, Junk Publishers, 1982.

6. ———: Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy. Am. J. Ophthalmol. 111:34, 1991.

7. Nishimura, M., Oka, Y., Takagi, I., Yamana, T., and Kitano, A.: The clinical features and treatment of the retinopathy of Bloch-Sulzberger syndrome (incontinentia pigmenti). Jpn. J. Ophthalmol. 24:310, 1980.

Reply

EDITOR:

The central concept addressed by Dr. van Nouhuys is as follows: "Could the fibrovascular tissue seen in our patient have a retinovascular rather than hyaloidal origin?" Three observations are used to support this concept: rapid postnatal development of the disease in some patients; poor vascular supply to the retina, possibly leading to ischemia and therefore a stimulus for retinal neovascularization; and diseases such as retinopathy of prematurity, familial exudative vitreoretinopathy, and incontinentia pigmenti are associated with retinovascular neovascularization. A secondary point raised by Dr. van Nouhuys is the issue of avascular retina in familial exudative vitreoretinopathy.

We believed we would find that the fibrovascular retrolental tissue would have a retinal origin and were surprised at surgery not only to find no true vascular connection to the retina but that the retina was truly avascular (that is, having no vessels anywhere as opposed to peripheral avascular retina in familial exudative vitreoretinopathy and retinopathy of prematurity). This led us to conclude that there was no retinovascular tissue in the scar but rather that it was composed of tissues derived from the hyaloid system and primary vitreous. The histologic findings confirmed our clinical impression of avascular retina. Because both vascular systems arise from common development origins, the issue became less critical. We agree the tissue represents an abnormal proliferation that could continue to some extent after birth because of secondary changes occurring in the scar.

A second issue is raised by Dr. van Nouhuys. Avascular developing retina is ischemic and therefore may provide a stimulus to a neovascular proliferation, as has been suggested in proliferative diabetic retinopathy. This has also been proposed in prematurity of retinopathy; however, in prematurity of retinopathy the evidence that immature avascular retina is hypoxic is lacking. First, the major oxygen consumer in normal retina is the photoreceptor, and in immature retina, as in retinopathy of prematurity and our patient, the photoreceptors have not developed. Secondly, usually immature retina is thin and therefore may be adequately supplied by the choroidal vasculature as is the case in animals such as the rabbit and horse. Finally, usually ischemia is evident histologically by cellular changes such as retinal edema, vascularization, and cell disruption. None of these signs were evident in our patient and are not typically present in retinopathy of prematurity. Although we do not believe ischemia is the cause of proliferation in our patient, other factors associated with normal vascular development gone astray might be operative.

We cannot fully answer the questions raised by Dr. van Nouhuys, but we believe they might stimulate investigations into this interesting controversy.

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Unilateral Frosted Branch Angiitis

EDITOR:

We read with interest the article, "Unilateral frosted branch angiitis," by S. L. Sugin, D. E. Henderly, S. M. Friedman, L. M. Jampol, and J. W. Doyle (Am. J. Ophthalmol. 111:682, June 1991). The authors state that " . . . the dramatic and apparently permanent resolution of the vasculitis after instituting systemic corticosteroids makes early, accurate diagnosis and institution of corticosteroids imperative." Our recent experience with a case of bilateral frosted branch angiitis suggests that the natural progression of this condition is variable and that such treatment is not always essential.

A 33-year-old, previously healthy, black woman had a one-week history of fever to 101 F, back pain, and headache. Orally administered erythromycin was prescribed. Two days before initial ophthalmologic examination she developed blurry vision in both eyes. On examination, she had a visual acuity of 20/400 in both eyes. The intraocular pressures were normal and the anterior segments were normal. Ophthalmoscopy showed healthy optic disks in both eyes with no disk edema or hemorrhages. There was extensive bilateral perivascular creamy white sheathing, affecting the veins more than the arteries, predominantly in the posterior poles (Fig. 1). Although there was sheathing present in all quadrants of both eyes, the superior retina was more severely affected in the right eye and the inferior retina in the left eye. The vitreous was clear. There were scattered retinal hemorrhages and marked central macular edema in both eyes. Fluorescein angiography showed marked late staining along the vessels, especially the veins, and no evidence of large or small vessel occlusions (Fig. 2). No treatment was prescribed. Three days later, mild anterior uveitis had developed. Results of the remainder of the examination were unchanged. Corticosteroids (topically applied every two hours) and cycloplegic eyedrops were prescribed. One week later, visual acuity improved to 20/70 in both eyes, the anterior uveitis was reduced, and there was much less retinal vascular sheathing. The systemic symptoms had resolved. The corticosteroid eyedrops were gradually tapered. Four weeks after initial manifestation visual acuity was 20/30 in both eyes. There was no anterior uveitis. The vascular sheathing and macular edema were almost completely resolved bilaterally. At no time were corticosteroids given systemically.

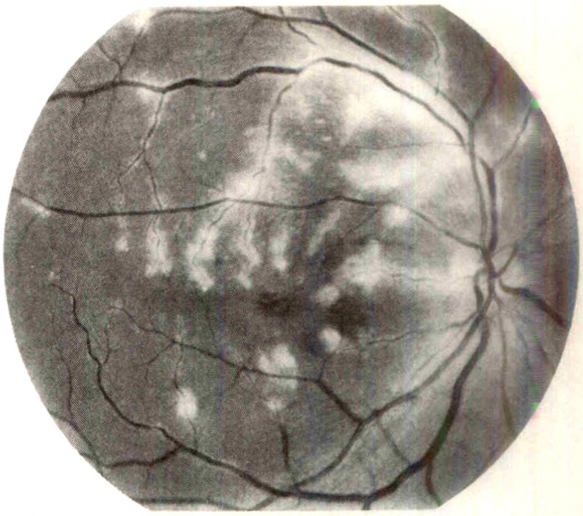

Fig. 1 (Vander and Masciulli). Red-free photograph of the right eye shows extensive sheathing of the retinal vessels, more pronounced in the superior macula.

The systemic work-up initiated at the time of the patient's first examination included the following: complete blood cell count, urinalysis, blood cultures, rapid plasma reagin, fluorescent titer antibody, sedimentation rate, sickle cell preparation, antinuclear antibody, Lyme, toxoplasmosis, human immunodeficiency virus, rheumatoid factor, cytomegalovirus, tu-

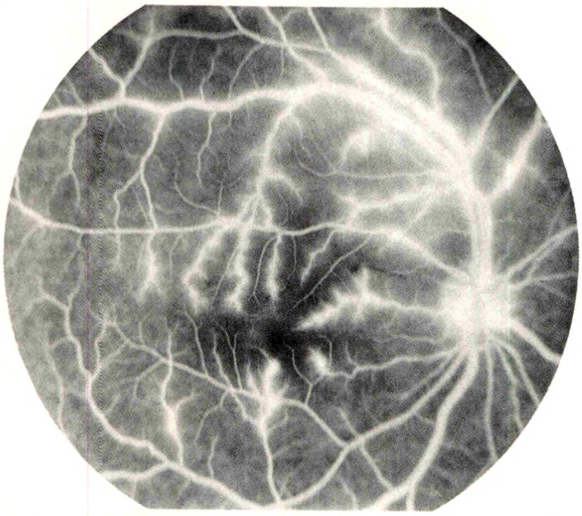

Fig. 2 (Vander and Masciulli). Early recirculation phase of the fluorescein angiogram shows extensive staining of the vessel walls, with the veins affected more than the arteries. There is no evidence of vaso-occlusive disease. Later views showed more leakage with diffusion of dye.

berculin skin testing, chest x-ray, liver function studies, glucose, and protein electrophoresis. Results of all of these studies were negative.

In their article, Dr. Sugin and colleagues state that visual recovery in cases of frosted branch angiitis can be limited by permanent macular abnormalities and, therefore, they suggest prompt institution of systemic corticosteroid therapy to prevent this complication. As in at least one other report cited,[1] however, development of macular scarring occurred in a patient who was treated systemically with corticosteroids. This is not to suggest that the corticosteroid treatment caused the scarring. Nor can we deny that the corticosteroids may have prevented more severe scarring that might have otherwise occurred. We simply would like to emphasize the point Sugin and colleagues make that " . . . the natural progression of the disease without corticosteroids is not well delineated . . ." Our patient had the typical ophthalmoscopic and angiographic features of this condition and has recovered dramatically without systemic corticosteroid therapy.

There is a strong temptation to initiate some form of treatment in cases of sudden, severe vision loss, especially when it occurs bilaterally. Although a short course of systemic corticosteroids is usually well tolerated, the potential for serious side effects does exist. This is especially true when the treatment extends over several weeks, as in this and other reports.[1,2] In this inflammatory condition of uncertain cause, corticosteroid therapy is a rational approach that may be very helpful in the recovery of vision. There does not appear to be sufficient evidence, though, to state that the institution of systemic corticosteroid therapy is "imperative."

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References

1. Kleiner, R. C., Kaplan, H. J., Shakin, J. L., Yannuzzi, L. A., Crosswell, H. H., Jr., and McLean, W. C., Jr.: Acute frosted retinal periphlebitis. Am. J. Ophthalmol. 106:27, 1988.
2. Watanabe, Y., Takeda, N., and Adachi-Usami, E.: A case of frosted branch angiitis. Br. J. Ophthalmol. 71:553, 1987.

The Comparative In Vitro Activity of Ofloxacin and Selected Ophthalmic Antimicrobial Agents Against Ocular Bacterial Isolates—Correction

EDITOR:

Our study evaluating the in vitro activity of ofloxacin vs norfloxacin, tobramycin, gentamicin, chloramphenicol, and polymyxin B against ocular pathogens[1] was one of the first studies evaluating the in vitro activity of the fluoroquinolone antiinfective, ofloxacin, against bacteria isolated only from ocular sources.

We had occasion to re-examine the in vitro data for polymyxin B as part of our preparation for a new in vitro study evaluating the activity of polymyxin B and trimethoprim against ocular bacterial strains. During the examination of our own data, we found an error that caused polymyxin B activity to be far less than necessary for proper in vitro evaluation.

The preparation of polymyxin B test solution requires conversion from units to milligrams of drug to determine the percent of polymyxin B activity in the solution. In our examination of the protocols for preparation of polymyxin B solution, we found a calculation error that caused a tenfold reduction in polymyxin B activity at one of the study sites. Specifically, a division error was made so that only one tenth of the polymyxin B necessary to make the test solution was added. As a result, the minimum inhibitory concentration (MIC) determinations for polymyxin B by modified tube-dilation procedures reported in our previous study are incorrect. For example, if the MIC value for a particular ocular strain was 16 μg/ml, that test tube actually contained only one tenth that concentration, or 1.6 μg/ml of polymyxin B.

Polymyxin B has been used in the treatment of ocular infections for many years in such combination products as Neosporin. Polymyxin B is rapidly bactericidal against gram-negative bacteria, including the serious ocular pathogen *Pseudomonas aeruginosa.* Polymyxin B kills bacteria by interfering with their cell membrane function. The MIC_{90} values for polymyxin B against *P. aeruginosa* from other published studies range from 1 to 2 μg/ml.[2,3] These values are considerably lower than those reported in our study because of the calculation error.

We are confident this unfortunate error did not have any impact on the other study medications or results because it was solely an error in the preparation of polymyxin B test solution. We apologize for this error and regret any confusion it may have caused.

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References

1. Osato, M. S., Jensen, H. G. Trousdale, M. D., Bosso, J. A., Borrmann, L. R., Frank, J., and Akers, P.: The comparative in vitro activity of ofloxacin and selected ophthalmic antimicrobial agents against ocular bacterial isolates. Am. J. Ophthalmol. 108:380, 1989.
2. Shungu, D. L., Tutlane, V. K., Weinberg, E., and Gadebusch, H. H.: In vitro antibacterial activity of norfloxacin and other agents against ocular pathogens. Chemotherapy 31:112, 1985.
3. Goldstein, E. J. G., Citron, D. M., Bendon, L., Vagvolgyi, A. E., Trousdale, M. D., and Appleman, M. D.: Potential of topical norfloxacin therapy. Comparative in vitro activity against clinical ocular bacterial isolates. Arch. Ophthalmol. 105:991, 1987.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Books Received

Color Vision Deficiencies. Edited by Y. Ohta. New York, Kugler Publications, 1990. 267 pages, index, illustrated. $70

These are the proceedings of the International Research Group on Color Vision Defects. The symposium was held in Tokyo in March 1990, a satellite of the 26th International Congress of Ophthalmology in Singapore. Thirty-one papers are published in this volume.

Distribution of Cataracts in the Population and Influencing Factors. Edited by K. Sasaki and O. Hockwin. Switzerland, Karger, 1991. 181 pages, index, illustrated. $148

This is the record of a symposium held in association with the 26th International Congress of Ophthalmology in March 1990. The subject is the epidemiology of cataracts. There are 27 papers, most of them on the prevalence of cataract and risk-factor determination.

Manual of Ocular Diagnosis and Therapy. Edited by Deborah Pavan-Langston. Boston, Little, Brown and Company, 1991. 494 pages, index, illustrated. $24.50

This is an updated edition of a spiral-bound pocket book that categorizes, summarizes, and outlines ophthalmic knowledge. It has been popular with medical students, emergency-room physicians, and house officers of all kinds. It lies flat where it has been opened, which somehow implies that the physician using it will have both hands occupied.

Neurological Organization of Ocular Movement. Edited by R. Daroff and A. Neetens. New York, Kugler Publications, 1990. 562 pages, index, illustrated. $135

This important book for neuro-ophthalmologists summarizes the current views of the leaders in clinical ocular movement research. It contains 22 review papers.

Night Vision: Basic, Clinical and Applied Aspects. Edited by R. F. Hess, L. T. Sharpe, and K. Nordby. Port Chester, New York, Cambridge University Press, 1990. 550 pages, index, illustrated. $120

Anyone interested in achromatopsia, or the process of dark adaptation, or the human rod visual system should have this book. Nordby and Sharpe's review of total color blindness, and Nordby's personal account of how he and his siblings grew up with central scotomas, an aversion to light, and total achromatopsia are excellent. Scientists will value this book because the chapters are richly documented (more than 1,200 references), and the index is excellent.

Perimetry Update 1990/1991. Edited by Richard P. Mills and Anders Heijl. New York, Kugler Publications, 1991. 585 pages, index, illustrated. $175.

Every two years the papers presented at the meeting of the International Perimetric Society are brought together in a volume. This series has become an important vehicle for papers about visual fields because it goes to all members of the society and to most medical libraries. If you want to keep up on perimetry, this is a compact way to do it. There are 93 papers in this volume.

Pupillenreaktionen-Pupillenstorungen. By Helmut Wilhelm. Stuttgart, W. Kohlhammer Druckerei GmbH & Co., 1991. 194 pages, index, illustrated. Price not given.

This little book, pictures and all, was crisply laid out by the author on his Macintosh computer. It is full of fresh diagrams and clear thinking about clinical pupillary problems. Any resident with even a smattering of German will learn a lot from it.

The Book List

Amblyopia: Basic and Clinical Aspects. By Kenneth J. Ciuffreda, Dennis M. Levi, and Arkady Selenow. Stoneham, MA, Butterworth Heinemann, 1991. 507 pages, index, illustrated. $75

Noninvasive Diagnostic Techniques in Ophthalmology. Edited by Barry R. Masters. New York, Springer-Verlag, Inc., 1990. 649 pages, index, illustrated. $149

Obituary

HARVEY Z. KLEIN

1931–1991

Ophthalmology has lost one of its truly gentle men. Harvey Z. Klein died July 11, 1991, after a protracted course of lymphatic leukemia. He leaves behind the legacy of a devoted husband and father, a dedicated physician and teacher, and a highly respected colleague to those of us who were fortunate enough to have known him.

Dr. Klein grew up in Pittsburgh, where he received a Bachelor of Science degree from the University of Pittsburgh in 1952. Upon graduating from medical school at the University of Buffalo and completing his internship in Pittsburgh, he served in the United States Navy from 1958 to 1961. After his honorable discharge, he entered Drexel Institute of Technology, where he earned a Master of Science in Biomedical Engineering, before going to the University of Chicago for his ophthalmology residency in 1963.

With his wife, Jean, and children, Merian and Lorin, the family settled in a suburb of Chicago. Seventeen years later, Dr. Klein left a successful private practice to enter academic medicine. He completed a retina fellowship at the Manhattan Eye and Ear Hospital and a glaucoma fellowship at the Duke University Eye Center before returning to Chicago in 1983, where he served on the faculties of both the University of Chicago and the University of Illinois. Although he was ill and receiving chemotherapy for most of this time, he served with distinction as a clinician and teacher.

Dr. Klein was a highly intelligent, thoroughly honest man, who made significant contributions to ophthalmology through his writings and lectures. However, his retiring, humble nature was such that his stature was not widely recognized. An example is his course on gonioscopy, which Ramesh Tripathi and I had the privilege of giving with him at the annual meeting of the American Academy of Ophthalmology for five years. Although this successful course was conceived of and coordinated by Dr. Klein, he insisted on giving the majority of the time and attention to Dr. Tripathi and to me.

Dr. Klein had many endearing traits. His quiet nature belied a marvelous sense of humor. He enjoyed telling a good story, although he would often laugh so hard that he could never make it to the punch line. I never did hear the end of one story, which he tried to tell on several occasions while at Duke. He also loved life in all its forms. I have it on good authority that, when an insect would stray into his house, he would take great care to usher it safely out and give it a second chance. When his dog was ill, he spent several hours every week driving it across town for special therapy.

Dr. Klein was remarkably compassionate with his patients, students, and colleagues. In his quiet way, he left this world a little better than he found it, and all of us whose lives he touched are better for having known him.

M. BRUCE SHIELDS

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Liberal benefits, conservative spending. The physicians for a national health program proposal. Grumbach, K.*, Bodenheimer, T., Himmelstein, D. U., Woolhandler, S.: JAMA 265:2549, 1991.

NATIONAL HEALTH INSURANCE PLAN

The Physicians for a National Health Program proposes to cover all Americans with one comprehensive public insurance program without copayments or deductibles and with free choice of provider. Such a national health program could reap tens of billions of dollars in administrative savings in the initial years, enough to fund generous increases in healthcare services not only for the uninsured, but for the underinsured as well. We delineate a transitional national health-program budget that would fix current overall health spending while accommodating increases in hospital and physician use. Future national health program spending would be indexed to the growth in gross national product adjusted for demographic, epidemiologic, and technologic shifts. Financing for the national health program would transfer funds into the public program without disrupting the general pattern of current revenue sources. We suggest a funding package that would augment existing government health spending with earmarked healthcare taxes. Because these new taxes would replace employer-employee insurance premiums and substantial portions of current out-of-pocket expenditures, they would not increase health costs for the average American.—Authors' abstract

*Physicians for a National Health Program, 1493 Cambridge St., Cambridge, MA 02139.

A call for action. The Pepper Commission's blueprint for health care reform. Rockefeller, IV, J. D.*: JAMA 265:2507, 1991.

NATIONAL HEALTH INSURANCE PLAN

After a year of deliberation and investigation, the Pepper Commission recommended action to ensure that all Americans would have health insurance protection in an efficient, effective health care system. Because it believes that action is urgent, the commission would build universal coverage by securing, improving, and extending the combination of job-based and public coverage we now have. Reform would entail the following elements: a combination of incentives and requirements that would guarantee all workers (with their nonworking dependents) insurance coverage through their jobs; replacement of Medicaid with a new federal program that would cover all those not covered through the workplace and workers whose employers find public coverage more affordable; guaranteed affordable coverage for employers—through reform of private insurance, tax credits for small employers, and the opportunity to purchase public coverage; a minimum benefit standard for private and public plans that would cover preventive and primary services as well as catastrophic care and would include cost sharing, subject to ability to pay; and a combination of public and private sector initiatives to promote quality and contain costs.—Author's abstract

*109 Hart, Senate Office Bldg., U.S. Senate, Washington, DC 20510.

Uncompensated and discounted Medicaid care provided by physician group practices in Wisconsin. Dunham, N. C.*, Kindig, D. A., Lastiri-Quiros, S., Barham, M. T., Ramsay, P.: JAMA 265:2982, 1991.

CHARITY CARE, BAD DEBT, DISCOUNTED MEDICAID CARE

A survey of a sample of physician group practices in Wisconsin was undertaken to determine the amounts of charity care, bad debt, and discounted Medicaid care that were provided in 1988. Overall, the physician group practices in the sample reported dollar amounts of uncompensated care and discounted Medicaid care that averaged approximately 7.6% of their total billings for the year (1.6% of charity care, 3.0% of bad debt, and 3.0% of discounted Medicaid care). From the dollar totals reported, it was calculated that the individual physicians represented by this sample of group practices were responsible for, on average, $4,300 of charity care, $9,100 of bad debt, and $7,500 of Medicaid discounted services, for a yearly per-physician total of $20,900 of uncompensated care and discounted care provided to uninsured and indigent patients. The results indicate that a majority of the group practices provided more charity care in 1988 than they had 5 years earlier and suggest that the burden of providing uncompensated care tends to fall disproportionately on those group practices that are also providing relatively high levels of service to Medicaid recipients.—Authors' abstract

*St. Marys Hospital Medical Center, 707 S. Mills St., Madison, WI 53715-0450.

Qui Tam: Suing physicians who make false claims.

Hsia, D. C.*: Ann. Intern. Med. 114:1050, 1991.

FALSE CLAIMS, QUI TAM ACTION

The 1986 False Claims Act Amendments authorized private citizens to sue on behalf of the U.S. government to recover federal funds from fraudulent recipients. The relator receives a share of any proceeds from a successful lawsuit. Originally enacted because of defense procurement scandals, this statute also applies to federal payments for health care, including Medicare, Medicaid, Civilian Health and Medical Program for Uniformed Services payments, veterans benefits, and research grants. In a recent Medicare upcoding case, the relator received approximately 25% of the $3.2 million settlement. Physicians can expect such litigation to increase in the future.—Michael A. Kass

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National outcomes of cataract extraction I. Retinal detachment after inpatient surgery.

Javitt, J. C.*, Vitale, S., Canner, J. K., Krakauer, H., McBean, A. M., Sommer, A.: Ophthalmology 98:895, 1991.

RETINAL DETACHMENT, CATARACT EXTRACTION

Rehospitalization for retinal detachment was studied in 338,141 Medicare beneficiaries older than 65 years of age who underwent inpatient cataract extraction in 1984. Extracapsular cataract extraction was performed in 202,847 of 338,141 patients (60%), intracapsular cataract extraction in 31%, and phacoemulsification in 9%. The risk of rehospitalization for retinal detachment within four years of intracapsular cataract surgery was 1.55%; the risk associated with extracapsular cataract surgery was 0.9%. The risk of retinal detachment after phacoemulsification was 1.17%. Cataract surgery accompanied by anterior vitrectomy was associated with a 5.0% likelihood of retinal detachment within four years. White patients were 1.7 times more likely to be rehospitalized for retinal detachment than were black patients (1.15% vs. 0.67%, $P < .001$). In both races, younger patients were more likely to be rehospitalized for retinal detachment than were older patients.—Michael A. Kass

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Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts.

The Italian-American Cataract Study Group*: Am. J. Epidemiol. 133:541, 1991.

CATARACT, CORTICOSTEROID USAGE, SUNLIGHT EXPOSURE

A total of 1,008 cases and 469 controls, aged 45–79 years, were included in a clinic-based case-control study of age-related cataract in Parma, Italy, from 1987 to 1989. Associations were examined between specific types of cataract and physiologic, behavioral, environmental, and biochemical factors. Cases included subjects with pure cortical (n = 489), pure nuclear (n = 110), pure posterior subcapsular (n = 28), and mixed (n = 381) cataracts. With polychotomous logistic regression, an increased risk of cataract was found for females (cortical; odds ratio (OR) = 2.20) and persons with less than a high school education (all types; OR = 1.53), brown irises (nuclear, mixed; OR = 1.43), job locations in the sunlight (cortical, mixed; OR = 1.75), leisure time activities in the sunlight (cortical, mixed; OR = 1.45), a history of wearing a hat in summertime (posterior subcapsular, cortical, mixed; OR = 1.80), a positive family history of cataract (posterior subcapsular, cortical, mixed; OR = 1.88), a history of cortisone use (posterior subcapsular;

OR = 8.39), increased red blood cell glucose-6-phosphate dehydrogenase activity (cortical, nuclear, mixed; OR = 1.36), and increased serum levels of uric acid (posterior subcapsular; OR = 1.62), lactic dehydrogenase (posterior subcapsular; OR = 1.76) and gamma-glutamyl transpeptidase (mixed; OR = 1.22). A decreased risk of cataract was found for persons with a positive history of arthritis (posterior subcapsular, nuclear, mixed; OR = 0.56) and increased handgrip strength (mixed; OR = 0.68). Findings from our study, combined with previously reported evidence, suggest that associations with educational status, cortisone use, sunlight exposure, and handgrip strength are real. Other findings require further evaluation.—Authors' abstract

*Dr. Giovanni Maraini, Institute of Ophthalmology, University of Parma, Via Gramsci 14, 43100 Parma, Italy.

Long-term follow-up of diabetic retinopathy for up to 71 months after combined renal and pancreatic transplantation. Ulbig, M.*, Kampik, A., Thurau, S., Landgraf, R., Land, W.: Graefe's Arch. Clin. Exp. Ophthalmol. 229:242, 1991.

DIABETIC RETINOPATHY, VITREOUS HEMORRHAGE, COMBINED RENAL AND PANCREATIC TRANSPLANTATION FOR DIABETES MELLITUS

Twenty-five patients (41 eyes, nine one-eyed patients), who had undergone successful renal and pancreatic transplantation, were examined for diabetic retinopathy. The mean duration of follow-up was 38 months (range, 15 to 71 months). All patients had undergone hemodialysis for advanced diabetic microvascular disease before transplantation and 30 of 41 eyes (74%) had advanced proliferative diabetic retinopathy. Visual acuity improved in 13 eyes (32%), remained stable in 19 (46%), and deteriorated in 9 (22%). Only two of the nine eyes that deteriorated sustained severe visual loss according to the definition of the Diabetic Retinopathy Study Group. The frequency and severity of vitreous hemorrhage improved in 19 eyes (46%), remained unchanged in 18 (44%), and worsened in four (10%). The authors concluded that combined renal and pancreatic transplantation was more effective in retaining vision in this group of patients who had severe proliferative diabetic retinopathy than were other modes of treatment, such as intensified conventional insulin therapy and artificial insulin delivery systems.—Michael A. Kass

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Glioblastomas in New England ophthalmologists. Bakshi, R.*, Ducatman A. M., Hochberg, F. H.: N. Engl. J. Med. 324:1440, 1991.

GLIOBLASTOMA, OPHTHALMOLOGISTS

A review of the neuropathology records at the Massachusetts General Hospital disclose three ophthalmologists who had been hospitalized since 1985 for histopathologically confirmed intracranial glioblastoma multiforme. Two of the ophthalmologists practiced in New Hampshire and one in Massachusetts. When a questionnaire was sent to members of the New England Ophthalmological Society, recently diagnosed glioblastoma was disclosed in one other ophthalmologist and in an ophthalmic nurse from New England. An increased risk of glioma has been suggested in other health-care professionals, including dentists, anatomists, and pathologists. Possible causes include papovavirus exposure, as well as exposure to industrial chemicals and nonionizing electromagnetic fields. Although the prevalence of glioblastoma in New England ophthalmologists may reflect chance occurrence or ascertainment bias, it is possible that ophthalmologists are at increased risk for glioblastoma because of exposure to an environmental factor in the workplace.—Michael A. Kass

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Detection of herpes simplex virus thymidine kinase and latency-associated transcript gene sequences in human herpetic corneas by polymerase chain reaction amplification. Rong, B.-L., Pavan-Langston, D., Weng, Q.-P., Martinez, R., Cherry, J. M., Dunke, E. C.*: Invest. Ophthalmol. Vis. Sci. 32:1808, 1991.

HERPES SIMPLEX, LATENT INFECTION, EXTRANEURONAL CORNEAL LATENCY

Herpes simplex virus type 1 is well established as a cause of latent infections in neurons and intermittently causes recurrent lesions at peripheral sites, such as the skin and eye. A number of authors have postulated extraneuronal latency of herpes simplex virus. A recently developed technique, polymerase chain reaction, allows for selective amplification of a given sequence of DNA. To investigate the possibility of extraneuronal latency during ocular herpes simplex virus infection, corneal specimens from 18 patients with quiescent herpes simplex keratitis were obtained at the time of keratoplasty. Polymerase chain reaction amplification and southern blot hybridization with a radiolabeled oligonucleotide probe were performed to detect the presence of herpes simplex virus type 1 genome in these human corneal samples. Two pairs of oligonucleotides from the region of the herpes simplex virus thymidine kinase gene and the latency-associated transcript gene were used as primers in the polymerase chain reaction amplification. The DNA sequences from either the thymidine kinase or the latency-associated transcript gene were identified in 15 of 18 herpes simplex keratitis corneas (83%). These results demonstrated the retention of herpes simplex virus genome, at least in part, in human corneas during quiescent herpes simplex virus infection, giving further support to the concept of corneal extraneuronal latency.—Michael A. Kass

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Corneal deposits associated with flecainide.

Møller, H. U.*, Thygesen K., Kruit P. J.: Br. Med. J. 302:506, 1991.

FLECAINIDE, CORNEAL DEPOSITS

Flecainide is a potent antiarrhythmic drug that is used for the treatment of ventricular and supraventricular tachycardias. Many patients treated with flecainide have complained of visual disturbances. Up to now this has been ascribed to an effect of flecainide on the ciliary muscle. The authors describe two patients who were treated with 100 to 300 mg of flecainide daily for four to six months. One patient developed photophobia, blurring and glare, whereas the other patient simply developed decreased visual acuity. Slit-lamp examination disclosed a gray whorl-shaped configuration in the cornea with a clear central area in both patients. Flecainide treatment was discontinued in both patients and visual acuity improved within several weeks. In one case corneal epithelium was removed and examined by means of high-pressure liquid chromatography. The specimen contained a substance that had the same chromatographic appearance as flecainide.—Michael A. Kass

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Use of cyclosporin in the management of steroid dependent non-necrotising scleritis.

Hakin, K. N., Ham, J., Lightman, S. L.*: Br. J. Ophthalmol. 75:340, 1991.

SCLERITIS, CORTICOSTEROID SIDE EFFECTS, CYCLOSPORIN

Five patients with non-necrotizing scleritis were treated with a combination of nonsteroidal anti-inflammatory drugs and systemic corticosteroids. The patients ranged in age from 21 to 64 years. One patient had Crohn's disease and one had nasal cartilage collapse possibly indicative of relapsing polychondritis. The other three patients were healthy. In four patients, satisfactory control of the ocular inflammation was achieved with doses of corticosteroids, but the disease relapsed when the dose was reduced. A fifth patient developed intolerable side effects from corticosteroids. All patients were then treated with cyclosporin A (5 mg/kg of body weight/day in two divided doses). After one to two weeks of combination therapy, the corticosteroid dose was gradually reduced. In all five patients the concurrent use of cyclosporin allowed the daily dose of prednisolone to be reduced. Three patients had relapses that were eventually controlled with a decreased daily dose of corticosteroid. Two patients managed to stop all treatment, one after seven weeks, the other after eight months of cyclosporin treatment. No detectable renal complications from the use of cyclosporin were observed as judged by the serum creatinine concentration. Hirsutism in one patient was the only side effect. Cyclosporin works by selectively inhibiting lymphokine secretion by activated T-cells. The effectiveness of cyclosporin in the treatment of scleritis suggests that T-cells are involved in the pathogenesis of the scleral inflammation.—Michael A. Kass

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Neuro-ophthalmologic signs of AIDS: 50 patients. Keane, J. R.*: Neurology 41:841, 1991.

AIDS, EYE MOVEMENT LIMITATION, DECREASED VISION

The author examined 50 hospitalized patients with acquired immunodeficiency syndrome. The patients ranged in age from 23 to 62 years. Forty-seven of the 50 patients were male. Eighteen patients had visual abnormalities, including eight with papilledema, four with optic neuropathy, and six with homonymous visual field defects. Fifteen patients had peripheral ocular motor involvement, including seven patients with unilateral sixth-nerve palsy, four with bilateral sixth-nerve palsy, five with unilateral third-nerve paresis, one with a bilateral third-nerve paresis, and one with a fourth-nerve palsy. Central eye movement limitations were observed in 17 patients. Meningitis usually caused by lymphoma or cryptococcus infection was the usual cause of peripheral nervous system involvement. Toxoplasmosis was the most common cause of central nervous system dysfunction.—Michael A. Kass

*1200 N. State St., Los Angeles, CA 90033.

Treatment of acute migraine with subcutaneous sumatriptan. Cady, R. K.*, Wendt, J. K., Kirchner, J. R., Sargent, J. D., Rothrock, J. F., Skaggs, H., Jr.: JAMA 265:2831, 1991.

MIGRAINE, SUMATRIPTAN, 5-HT$_{1D}$ RECEPTOR AGONIST

Sumatriptan succinate, a 5-HT$_{1D}$ receptor agonist, constricts human cranial arteries. Two parallel-group trials for treatment of acute migraines were conducted in the United States. Adult patients were randomized and given either 6 mg of sumatriptan succinate subcutaneously (n = 734) or placebo (n = 370). At 1 hour, sumatriptan was significantly more effective than placebo in reducing moderate or severe headache pain to mild or no pain (70% vs 22%), in completely relieving headaches (49% vs 9%), and in improving clinical disability (76% vs 34%). Sumatriptan also reduced nausea and photophobia significantly better than placebo. Patients with residual migraines received another injection; those who had originally received sumatriptan received either a second active injection (n = 187) or placebo (n = 178), while those who had received placebo received a second placebo injection (n = 335). Statistical evidence for benefit of second sumatriptan injection is absent. Adverse events associated with sumatriptan were tingling, dizziness, warm-hot sensations, and injection-site reactions. Sumatriptan is effective and well tolerated in patients with acute migraine.—Authors' abstract

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NEWS ITEMS

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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Second International Symposium on Ocular Trauma

The Second International Symposium on Ocular Trauma will be held in Geneva, Switzerland, April 2–5, 1992. For additional information, write The Secretariat, Kouni, Travel Ltd., 7 Rue de Berne, P.O. Box 541, CH1211, Geneva 1, Switzerland.

University of Toronto: Update in Vitreoretinal Diseases

The University of Toronto will sponsor Update in Vitreoretinal Diseases, Feb. 21 and 22, 1992, at the Four Seasons Hotel in Toronto, Canada. For more information, write Dorcas Lam, Office of Continuing Education, Faculty of Medicine, University of Toronto, Medical Sciences Bldg., Toronto, Ontario M5S 1A8; telephone (416) 978-2718.

University of California at San Francisco: Management of Cranial Base Diseases

The University of California at San Francisco School of Medicine will sponsor a Multidisciplinary Panel on Skull Base Diseases at the Ritz Carlton Hotel in San Francisco, Nov. 10, 1991. For additional information, write Extended Programs in Medical Education, Rm. LS-105, University of California School of Medicine, San Francisco, CA 94143-0742; telephone (415) 476-4251.

Louisiana State University Eye Center: Fifth Ophthalmology Update 1991

The 5th Louisiana State University Eye Center Ophthalmology Update will be held Dec. 1–5, 1991, at the Ritz Carlton Mauna Lani, Hawaii. For further information, write Emily D. Varnell, LSU Eye Center, 2020 Gravier St., Ste. B, New Orleans, LA 70112; telephone (504) 568-6700 ext. 336.

New York Eye & Ear Infirmary: Corneal and External Diseases 1992

The New York Eye & Ear Infirmary will sponsor Corneal and External Diseases 1992: A Current Perspective, Dec. 6 and 7, 1991, in New York City. For more information, write Sylvia Sorrentino, The Institute for Continuing Medical Education, The New York Eye & Ear Infirmary, 2nd Ave. & 14th St., New York, NY 10003; telephone (212) 979-4444 or (212) 979-4430.

Retina Research & Development Foundation and Alcon Surgical, Inc.: Midwinter Laser Course and Fluorescein Angiography Workshop

The Retina Research & Development Foundation and Alcon Surgical, Inc. will sponsor the Midwinter Laser Course and Fluorescein Angiography Workshop, Feb. 7 and 8, 1992, in St. Louis, Missouri. For additional information, write Leigh Dundon, East Pavilion, One Barnes Hospital Plaza, Ste. 17413, St. Louis, MO 63110; telephone (314) 367-1181.

Sacramento Retina Society: Eleventh Annual Squaw Valley Retina Symposium

The Sacramento Retina Society will sponsor the Eleventh Annual Squaw Valley Retina Symposium at the Resort at Squaw Creek in California Jan. 31–Feb. 4, 1992. For more information, write Richard A. Murray, M.D., 2701 Eye St., Sacramento, CA 95816; telephone (916) 442-4975.

Scheie Eye Institute: Third Annual Symposium on Diabetic Complications

The Scheie Eye Institute at the University of Pennsylvania will hold the Third Annual Symposium on Diabetic Complications, Nov. 2, 1991. For more information, write Charlotte Beurer, Office of Continuing Medical Education, University of Pennsylvania, 51 N. 39th St., Philadelphia, PA 19104; telephone (215) 662-8141; fax (215) 662-0133.

Wilmer Ophthalmological Institute: Management of Diabetic Retinopathy

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor Management of Diabetic Retinopathy: Application of Guidelines from 1991 ETDRS Publications on Nov. 15, 1991, at the Johns Hopkins Medical Institutions. For further information, write Program Coordinator, Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 20, Baltimore, MD 21205-2195; telephone (301) 955-2959.

Ludwig Von Sallmann Prize: Tenth International Congress of Eye Research

The Ludwig Von Sallmann Prize will be awarded at the Tenth International Congress of Eye Research to be held Sept. 21–26, 1992, in Stresa, Italy. The award of $30,000 is for outstanding achievement in ophthalmology and vision. For more information and how to obtain nomination blanks, write Peter Gouras, M.D., Von Sallmann Prize Committee, Columbia University, Box 18, 630 W. 168 St., New York, NY 10032; telephone (212) 305-5688; fax (212) 305-3173.

Health and Welfare Canada: Advisory Committee on Excimer Laser

The following are members of the Advisory Committee on the Excimer Laser, Health and Welfare Canada: Marvin L. Kwitko, chairman, Montreal; Robert Read, Halifax; Gilles Marcil, Montreal; Jane Murphy, Toronto; Mervyn Kirker, Calgary; and Paul Dubord, Vancouver.

Personal

Carmen A. Puliafito

Carmen A. Puliafito, former director of the Morse Laser Center and president of the medical staff at the Massachusetts Eye and Ear Infirmary and associate professor of ophthalmology at Harvard Medical School, has been appointed ophthalmologist-in-chief at New England Eye Center and chairman of the Department of Ophthalmology at Tufts University School of Medicine.

Immunohistochemistry of Proteoglycans in Human Lamina Cribrosa

Victor L. Caparas, M.D., Charles Cintron, Ph.D.,
and M. Rosario Hernandez-Neufeld, D.D.S.

Proteoglycans are macromolecular components of connective tissue, which are believed to have an important role in the organization of other extracellular matrix components and in the hydration and rigidity of tissue. Using antibodies to the heparan sulfate-, dermatan sulfate-, and keratan sulfate-proteoglycans core proteins, we used indirect immunofluorescence to determine the presence of these core proteins and to characterize their distribution in the lamina cribrosa of healthy human eyes of various ages. Findings with heparan sulfate-proteoglycan core proteins support the multilayered organization of basement membranes in the lamina cribrosa as proposed in previous reports. Dermatan sulfate-proteoglycan core protein results indicate colocalization with fibrillar collagen. Application of monoclonal antibodies to the glycosaminoglycan side chain disclosed an increasing predominance of chondroitin-4-sulfate over chondroitin-6-sulfate with age. This may indicate a decreasing water-holding capacity of the cribriform plates and suggest a decreasing ability to withstand pressure. This study attempts to identify the core proteins of proteoglycans in human lamina cribrosa and serves as a basis for study of glaucomatous eyes.

OPTIC-NERVE FIBER INJURY in glaucoma has been localized to the lamina cribrosa.[1,2] Studies of human eyes with glaucoma have suggested the importance of the structural support provided by this tissue and its role in the damage of optic-nerve fibers after distortion of the cribriform plates.[1-6]

Differences in the connective-tissue composition of the optic-nerve head of patients with glaucoma may account for increased susceptibility to optic-nerve damage from increased intraocular pressure. Tengroth and Ammitzboll[7] found a higher proportion of collagen in lamina cribrosa of glaucomatous eyes than that in normal eyes. Immunohistochemical studies have demonstrated a difference in lamina cribrosa between healthy adult eyes and eyes with moderate-to-advanced glaucoma. The lamina cribrosa of glaucomatous eyes showed more marked changes in the organization and amounts of extracellular matrix components than did the healthy eyes, elastin and fibrillar collagen components in particular.[8-11] These changes may influence the supportive function of the lamina cribrosa, possibly leading to compromised viability of the nerve fibers.[5,9,10]

Among the components of extracellular matrix of lamina cribrosa are the proteoglycans. These highly acidic macromolecules consist of a protein backbone or core protein covalently attached to at least one sulfated glycosaminoglycan side chain. Glycosaminoglycans are composed of long carbohydrate chains that exist in the following four main forms: (1) dermatan sulfate and chondroitin sulfate; (2) keratan sulfate; (3) heparan sulfate and heparin; and (4) hyaluronic acid (which is not linked to a core protein and lacks a sulfate group). Through interactions of its core protein and glycosaminoglycan side chains with other macromolecular components of the extracellular matrix, the proteoglycans have an important role in the organization of connective tissue.[12] Heparan sulfate proteoglycan is a major constituent of basement membrane and as such is particularly important to the lamina cribrosa, which has been described as being structured of transversely oriented laminae.[13] Type-I collagen, previously demonstrated in the cribriform

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Reprint requests to Charles Cintron, Ph.D., Eye Research Institute, 20 Staniford St., Boston, MA 02114.

plates,[13-15] has been shown to bind to decorin, a ubiquitous, dermatan sulfate–containing proteoglycan.[16] Similarly, the core protein of keratan sulfate proteoglycan, which is in many tissues,[17] is believed to have a role in the spacing of collagen fibrils.

Of particular relevance to the mechanical support function of the lamina is the role proteoglycans may have in determining the rigidity of connective tissue. This property appears to be in part dependent on the glycosaminoglycan water-binding properties that, as has been seen in cartilage, endow the tissue with compressive stiffness and the ability to sustain repeated loading, that is, resiliency. Water-holding capacity in turn has been shown to be determined by glycosaminoglycan charge density and location of its negatively charged sulfate groups.[18-20]

Reports documenting the content and function of proteoglycans in the human lamina cribrosa have been few. Hernandez, Andrzejewska, and Neufeld[9] used antibody to the core protein of heparan sulfate proteoglycan to demonstrate thickening of basement membranes of cribriform plates in glaucomatous eyes. Preliminary reports have identified chondroitin sulfate,[21,22] keratan sulfate, hyaluronic acid, and heparan sulfate glycosaminoglycan side chains in human and primate eyes.[22,23] Information on the types and distribution of the core proteins of proteoglycans in the optic-nerve head has been scarce. Given the importance of the mediating role of the proteoglycans' component core proteins and glycosaminoglycan side chains in the interaction of the various macromolecules of the extracellular matrix, we attempted to identify the distribution of these molecules in lamina cribrosa of healthy human eyes, using immunohistochemical methods. An understanding of the distribution of the proteoglycans in normal and glaucomatous eyes may provide insight to their role in the function of the tissue and possible effect of the optic-nerve head's response to increased intraocular pressure.

Material and Methods

Seven pairs of eyes obtained from the New England Eye Bank were divided into the following groups by age: (1) young, 16 and 19 years old; (2) middle-aged, 56 and 57 years old; and (3) old, 78, 88, and 96 years old. All were obtained from white donors who had no history of ocular disease. Incidence of glaucoma in nonwhites was higher. Care was taken to use only eyes from white donors. All eyes were enucleated within four hours of death and processed within 24 hours. The optic-nerve head was cut and embedded in Tissue-Tek optimal cutting temperature compound (Miles Scientific, Elkhart, Indiana) and stored at −70 C until sectioning.

Serial 8-μm-thick cross sections and sagittal cryostat sections were obtained and applied onto formalin-fixed, gelatin-covered slides. These were then air-dried, and stored at −20 C.

Before staining, sections were dried for three hours at 37 C. These were then washed three times for three minutes each in phosphate-buffered saline solution containing 1.5% bovine serum albumin. Incubation in moist chambers for 30 minutes at 25 C was performed with the following antibodies: (1) polyclonal antibody core protein, dermatan sulfate proteoglycan, 1:100; (2) polyclonal antibody to core protein, keratan sulfate proteoglycan, 1:100; (3) monoclonal antibody to core protein, heparan sulfate proteoglycan (Chemicon, Temecula, California), 1:5; and (4) monoclonal antibodies to chondroitin; chondroitin-4-sulfate; and chondroitin-6-sulfate glycosaminoglycan side chains (ICN Biomedical Inc., Costa Mesa, California), 1:50.

Sections stained with the chondroitin, chondroitin-4-sulfate, and chondroitin-6-sulfate antibodies were digested with 0.5-unit/ml chondroitinase ABC lyase (ICN Biomedical Inc., Costa Mesa, California) for two hours at 37 C. The specificity of the dermatan sulfate-proteoglycan and keratan sulfate-proteoglycan core protein antibodies has been demonstrated by polyacrylamide-gel electrophoresis and Western blot analyses.[23] Specificities of the antibodies obtained commercially have been previously reported.[24,25]

Sections were incubated with the appropriate fluorescein- or rhodamine-conjugated secondary antibody for 30 minutes at 25 C in moist, light-protected chambers. Working dilution for fluorescein-isothiocyanate-conjugated rabbit anti-sheep IgG (Cappel, Malvern, Pennsylvania) was 1:500 and that of rhodamine-conjugated goat anti-mouse IgG and IgM (Cappel, Malvern, Pennsylvania) was 1:20. Double-immunofluorescence labeling was done by performing the following antibody incubation steps in succession: antibody to dermatan sulfate-proteoglycan core protein, antibody to chondroitin-4-sulfate, followed by the fluorescein- and rhodamine-conjugated secondary antibodies.

Sections incubated with the appropriate nonimmune serum as primary antibody and then incubated with either fluorescein- or rhodamine-conjugated secondary antibody served as controls. Observation and photography were performed with a microscope equipped with illumination and appropriate filter systems.

Results

Proteoglycans and glycosaminoglycans in sectioned human lamina cribrosa tissue are identified on the basis of differences (as compared to controls) in amount or pattern of immunofluorescence after incubation of the sections with the specific antibody to proteoglycan or glycosaminoglycan.

Dermatan sulfate-proteoglycan core protein—All eyes from all three age groups demonstrated staining of the cribriform plates with the polyclonal antibody to the core protein of dermatan sulfate proteoglycan. This appeared on cross sections as wavy, filamentous structures along the long axis and within the core of the cribriform plate (Fig. 1, top row) and on sagittal sections as horizontally disposed filamentous material in the cribriform plate substance (Fig. 2, left). The amount and density of the staining did not appear to differ from one age group to the other. Sclera, pial septa, and the intima of the central retinal arteriole stained brightly.

Keratan sulfate-proteoglycan core protein—No staining with the polyclonal antibody to the core protein of keratan sulfate proteoglycan was observed in the lamina cribrosa of all eyes of all age groups (Fig. 2, middle). Positive staining of the sclera (not shown) and walls of blood vessels was observed.

Heparan sulfate-proteoglycan core protein—Monoclonal antibody to the core protein of heparan sulfate proteoglycan stained cross sections of the lamina cribrosa of all age groups as a linear, but irregular, coating that separated nerve tissue from the surrounding connective tissue of the cribriform plates (Fig. 1, second row from top). Staining of the core of the plate showed a network of filamentous material along the long axis of the plate. In sagittal section, the pattern was of a well-defined stacking of lamellar structures (Fig. 2, right). The pial septa showed a similar coating of staining on cross section, but lacked the lamellar pattern seen in sagittal section. Blood vessels throughout the lamina cribrosa and adjacent tissues were positively stained. As an internal negative control, the scleral connective tissue was not stained (not shown). An age-related change in staining pattern was not observed.

Chondroitin—No staining of the cribriform plates appeared after incubation with this antibody (not shown). Sclera was heavily stained, providing an internal control.

Chondroitin-4-sulfate—Intense staining of the cribriform plates from eyes of all age groups was seen after incubation with antibody to 4-sulfated chondroitin glycosaminoglycan (Fig. 1, third row from top). Fine interweaving fibrils along the length of the plate were observed in the core of the cribriform plates. The staining pattern appeared to localize in the same area as that of the antibody to the core protein of dermatan sulfate proteoglycan. The density of staining appeared to increase with increasing age. Pial septa, blood vessel walls, and sclera (not shown) also stained brightly with the antibody.

Chondroitin-6-sulfate—A patchy, powdery staining of the substance of the cribriform plate was observed (Fig. 1, bottom row). The density of staining did not appear to change with increasing age. Sclera and blood vessels stained brightly with this antibody (not shown).

Double immunofluorescent labeling—Sections labeled with antibody to dermatan sulfate-proteoglycan core protein and chondroitin-4-sulfate were stained with fluorescein green (Fig. 3, left) and rhodamine red (Fig. 3, middle) secondary antibody. Double-exposure photography was performed, disclosing an orange-red hue in areas of overlapping stain (Fig. 3, right). We have interpreted this as an indicator of colocalization of the dermatan sulfate-proteoglycan core protein and chondroitin-4-sulfate.

Discussion

We examined the distribution of the proteoglycans in human lamina cribrosa by studying the immunohistochemical staining for the proteoglycans' two major domains of the core protein and the glycosaminoglycan side chain. Different core proteins of various proteoglycans, namely those of keratan sulfate proteoglycan, decorin, and basement-membrane heparan sulfate proteoglycan, have been identified in the ocular tissues of various species, but we attempted to identify those in humans.

Our results indicate core protein of heparan sulfate proteoglycans is present in basement membranes transversely layered across the op-

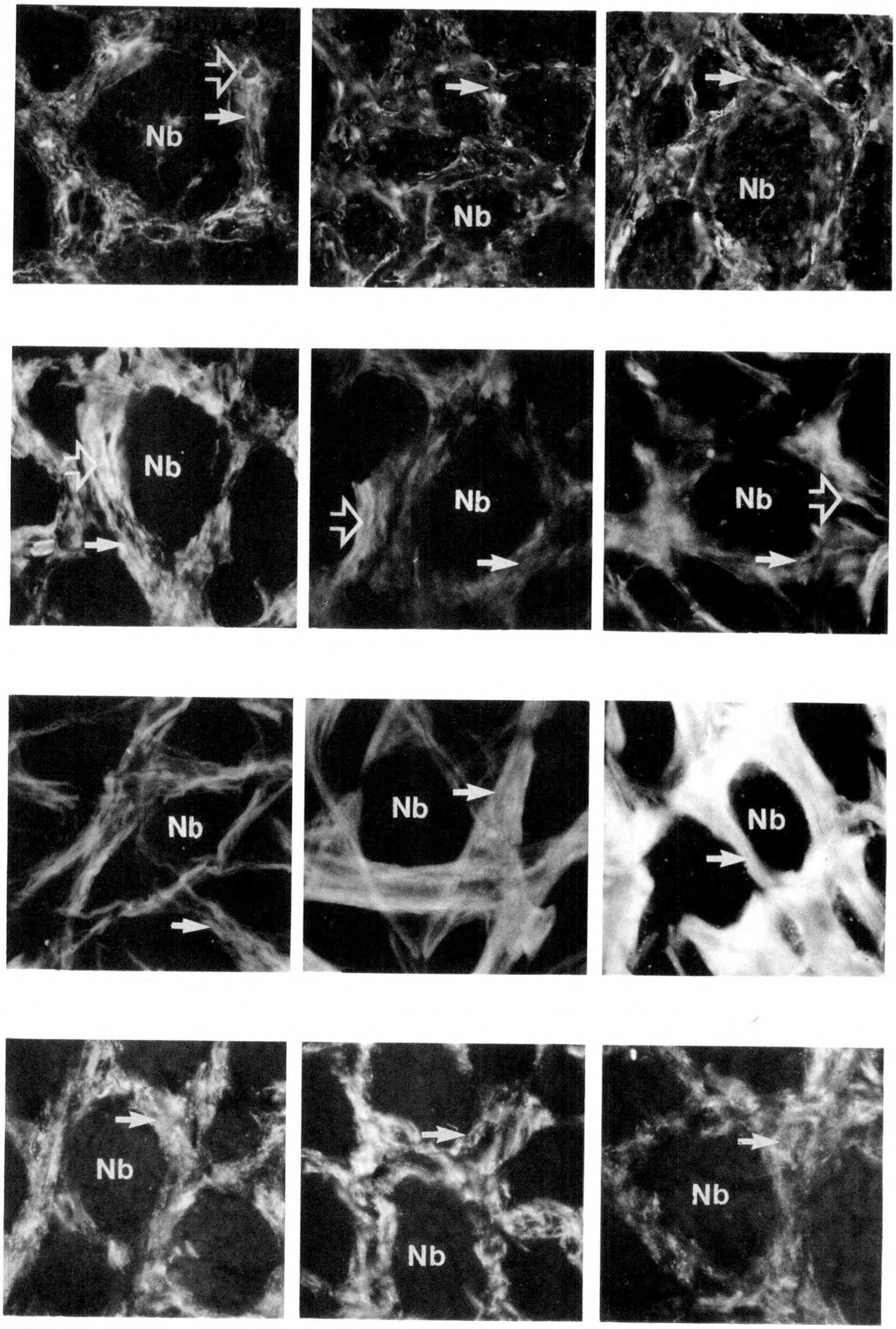

Fig. 1 (Caparas, Cintron, and Hernandez-Neufeld). Immunofluorescent staining of cross sections of lamina cribrosa from a 19-year-old man (left column), a 57-year-old woman (middle column), and an 88-year-old woman (right column; × 230). Top row, Staining for core protein of dermatan sulfate proteoglycan. No increase in staining for dermatan sulfate proteoglycan in the cribriform plate was apparent with increasing age. Notice staining of blood vessel wall. Second row from top, Staining for core protein of heparan sulfate proteoglycan. Notice staining in the core of the cribriform plate and of blood vessel walls. Third row from top, Staining for chondroitin-4-sulfate glycosaminoglycan. Notice marked increase in density of stained material with increasing age. Bottom row, Staining for chondroitin-6-sulfate glycosaminoglycan. An age-related increase in density of staining for this material was not observed. Nb indicates nerve bundle, solid arrow indicates stained material in cribriform plate, and arrow outline indicates blood vessel.

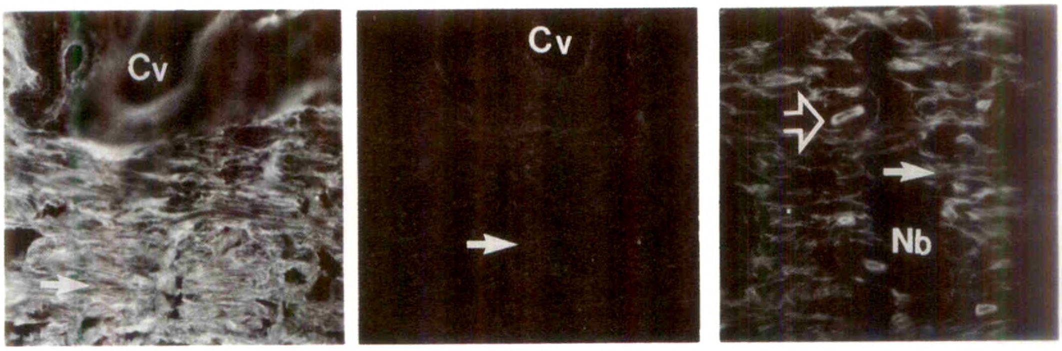

Fig. 2 (Caparas, Cintron, and Hernandez-Neufeld). Immunofluorescent staining in sagittal sections of lamina cribrosa of a 78-year-old woman (× 116). Left, Staining for core protein of dermatan sulfate proteoglycan. Middle, Staining for core protein of keratan sulfate proteoglycan. Notice absence of staining throughout lamina and only mild staining of blood vessel wall. Right, Staining for core protein of heparan sulfate proteoglycan. Notice transverse distribution of stained material. Cv indicates central retinal vessel, Nb indicates nerve bundle, solid arrow indicates cribriform plate, and arrow outline indicates blood vessel.

tic nerve and surrounding the nerve bundles. This pattern, and the apparent lack of an age-related increase, closely resemble the immunohistochemical staining pattern for type-IV collagen reported previously.[13,14] Both type-IV collagen and heparan sulfate proteoglycan are major constituents of basement membranes. Our findings strengthen the proposed model of a transversely oriented lamellar organization of the cribriform plates.[13]

Heparan sulfate proteoglycans may serve as conduits to orient sprouting nerve fibers and guide them to their targets.[26] Heparan sulfate proteoglycans may be involved in diverse functions in the nervous system such as synaptogenesis, cell motility, and association with neurotrophic factors.[26] They have been shown to act as a reservoir for fibroblast growth factor, and to bind with other growth factors such as Schwann cell-growth factor and a retinal survival factor.[27]

Decorin was found to stain in a fibrillar pattern occupying the core of the cribriform plate, similar to the pattern described for type-I collagen[8] and suggesting colocalization of the two molecules. However, we did not observe an age-related increase with decorin, which was in contrast to the previously reported marked age-related increase with type-I collagen.

Decorin is known to associate with type-I collagen through its core protein[28] and may influence the interfibrillar spacing of collagen. Moreover, this proteoglycan may also have a role in collagen fibril assembly.[16] If the proportion of decorin to type-I collagen does indeed change with age, the size and organization of

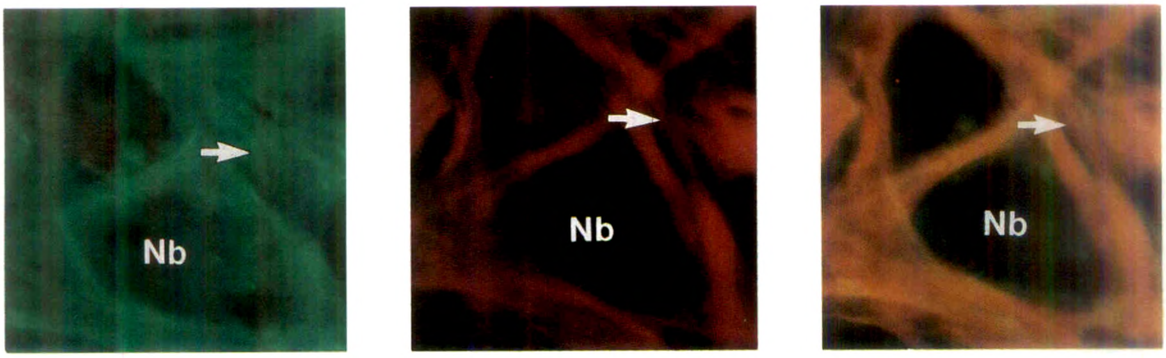

Fig. 3 (Caparas, Cintron, and Hernandez-Neufeld). Double immunofluorescent staining of a cross section of lamina cribrosa of 57-year-old (× 230). Left, Staining for core protein of dermatan sulfate proteoglycan (fluorescein label, green); middle, staining for chondroitin-4-sulfate glycosaminoglycan (rhodamine label, red); right, double exposure. Staining pattern suggests colocalization of the two antibodies. Nb indicates nerve bundle, and solid arrow indicates material stained for both antibodies in cribriform plate.

collagen fibrils in the lamina cribrosa may change with age as well. Because the primary function of type-I collagen fibrils in connective tissue is structural, alterations in their organization in the cribriform plate would have a marked effect on the mechanical strength of the tissue.

The lack of immunohistochemical evidence in this study for the core protein of keratan sulfate proteoglycan is not consistent with results of a biochemical analysis by Knepper and associates[29] reporting small quantities of keratan sulfate glycosaminoglycan in the lamina cribrosa. Our results, however, are supported by recent cytochemical studies by Fukuchi and associates.[30]

Although the lamina cribrosa did not stain for the core protein of keratan sulfate proteoglycan in all ages tested, adjacent sclera stained intensely (not shown), providing a convenient internal positive control. This sharp delineation between lamina cribrosa and sclera indicates a marked difference in the origin as well as in the functions of these two tissues. Similar to decorin, keratan sulfate proteoglycan interacts with collagen fibrils and is probably involved in collagen fibril spacing, tissue hydration, and rigidity. The lack of keratan sulfate proteoglycan in lamina cribrosa and its presence in sclera underscore the belief that the lamina cribrosa is a highly specialized tissue distinct from sclera in its physical properties.

Decorin contains a single dermatan-chondroitin sulfate glycosaminoglycan. Our results show that decorin core protein appears to colocalize with glycosaminoglycan containing 4-sulfated chondroitin in the lamina cribrosa. The age-related changes in 4-sulfated chondroitin on one hand and lack of changes in decorin on the other indicate that decorin either increases the number of glycosaminoglycan side chains or increases its chain length with age. Clearly, chemical analysis is needed to clarify the situation.

Bettelheim and Ehrlich[18] have shown the water-holding capacity of 4-sulfated chondroitin to be less than that of 6-sulfated chondroitin. This means that the 6-sulfated glycosaminoglycan gives up water less readily in response to an applied pressure, conferring to the tissue a more resilient quality. Highly hydrated tissues such as embryonic skin,[31] fetal cornea,[32] and healing adult corneas[33] have been shown to synthesize a higher proportion of 6-sulfated chondroitin glycosaminoglycan side chains compared to normal adult tissue in which 4-sulfated glycosaminoglycan side chains predominate. These differences underscore the importance of the sulfation of glycosaminoglycan side chains and indicate that the proportions of 4- and 6-sulfated chondroitin glycosaminoglycans within a tissue determine the degree of hydration and consequently, the rigidity of the tissue.

It is widely believed that the axonal damage observed in glaucoma results from the distortion of the lamina cribrosa by increased intraocular pressure. The age-related differences in the proportion of the component glycosaminoglycans that we have observed here may have bearing on the mechanical support provided by the lamina cribrosa. Our findings of an apparent increase in the proportion of 4-sulfated chondroitin in the cribriform plates of 78- to 96-year-old individuals indicate a decreasing water-holding capacity, and may indicate a less resilient lamina cribrosa perhaps more vulnerable to distortion by intraocular pressure. The various age-related changes in optic-nerve head connective tissue and the acknowledged increased incidence of primary open-angle glaucoma in older age groups argue for the role of age-related changes in connective tissue in the pathogenesis of glaucoma.

The physical characteristics endowed by the proteoglycans to tissue and their ability to participate in cellular interactions underscore the importance of this class of molecules. We attempted to identify the distribution of core proteins of proteoglycans in the lamina cribrosa. By first determining the distribution in the tissue, we hoped to establish baseline data on which further inquiry into the function of these proteoglycans may be based. Extension of this work to glaucomatous eyes is being undertaken and is hoped to elucidate further on the various questions raised in our study.

References

1. Quigley, H. A., Addicks, E. M., Green, W. R., and Maumenee, A. E.: Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Arch. Ophthalmol. 99:635, 1981.
2. Quigley, H. A.: Reappraisal of the mechanisms of glaucomatous optic nerve damage. Eye 1:318, 1987.
3. Radius, R. L., and Gonzales, M.: Anatomy of the lamina cribrosa in human eyes. Arch. Ophthalmol. 99:2159, 1981.
4. Quigley, H. A., Addicks, E. M.: Regional differ-

ences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. Arch. Ophthalmol. 99:137, 1981.

5. Zeimer, R. C., and Ogura, Y.: The relation between glaucomatous damage and optic nerve head mechanical compliance. Arch. Ophthalmol. 107:1232, 1989.

6. Zeimer, R. C., and Edward, D. P.: The possible viscoelastic etiology of glaucoma damage. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 565.

7. Tengroth, B., and Ammitzboll, T.: Changes in the content and composition of collagen in the glaucomatous eye. Basis for a new hypothesis for the pathogenesis of chronic open angle glaucoma. Acta Ophthalmol. 62:999, 1984.

8. Hernandez, M. R., Luo, X. X., Andrzejewska, W., and Neufeld, A. H.: Age-related changes in the extracellular matrix of the human optic nerve head. Am. J. Ophthalmol. 107:476, 1989.

9. Hernandez, M. R., Andrzejewska, W. M., and Neufeld, A. H.: Changes in the extracellular matrix of the human optic nerve head in primary open-angle glaucoma. Am. J. Ophthalmol. 109:180, 1990.

10. Morrison, J. C., Dorman-Pease, M. E., Dunkelberger, G. R., and Quigley, H. A.: Optic nerve head extracellular matrix in primary optic atrophy and experimental glaucoma. Arch. Ophthalmol. 108:1020, 1990.

11. Quigley, H. A., Dorman-Pease, M. E., Dunkelberger, G., and Brown, A.: Changes in collagen and elastin in the optic nerve head in chronic human and experimental monkey glaucoma. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 564.

12. Ruoslahti, E.: Proteoglycans in cell regulation. J. Biol. Chem. 264:13369, 1989.

13. Hernandez, M. R., Igoe, F., and Neufeld, A. H.: Extracellular matrix of the human optic nerve head. Am. J. Ophthalmol. 102:139, 1986.

14. Hernandez, M. R., Luo, X. X., Igoe, F., and Neufeld, A. H.: Extracellular matrix of the human lamina cribrosa. Am. J. Ophthalmol. 104:567, 1987.

15. Goldbaum, M. H., Jeng, S., Logemann, R., and Weinreb, R. N.: The extracellular matrix of the human optic nerve. Arch. Ophthalmol. 107:1225, 1989.

16. Vogel, K. G., Paulsson, M., and Heinegard, D.: Specific inhibition of type I and type II collagen fibrillogenesis by the small proteoglycan of tendon. Biochem. J. 223:587, 1984.

17. Funderburgh, J. L., Caterson, B., and Conrad, G. W.: Distribution of proteoglycans antigenically related to keratan sulfate proteoglycan. J. Biochem. 262:11634, 1987.

18. Bettelheim, F. A., and Ehrlich, S. H. A.: Water vapor sorption of mucopolysaccharides. J. Physiol. Chem. 67:1948, 1963.

19. Bettelheim, F. A., and Plessy, B.: The hydration of proteoglycans of bovine cornea. Biochim. Biophys. Acta 381:203, 1975.

20. Plessy, B., and Bettelheim, F. A.: Water vapor sorption of keratan sulfate. Mol. Cell. Biochem. 6:85, 1975.

21. Morrison, J. C., and Rask, P.: Immunohistochemical localization of chondroitin sulfate proteoglycans in the primate lamina cribrosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelpha, J. B. Lippincott, 1990, p. 455.

22. Steely, H. T., Wilson, K., Clark, A., and Knepper, P. A.: Biochemical similarities of human trabecular meshwork and lamina cribrosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 455.

23. Covington, H. I., Kublin, C. L., and Cintron, C.: Immunohistochemistry of keratan sulfate and dermatan sulfate in healing cornea. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 321.

24. Couchman, J. R., Caterson, B., Christner, J. E., and Baker, J. R.: Mapping by monoclonal antibody detection of glycosaminoglycans in connective tissues. Nature 307:650, 1984.

25. Kemeny, E., Fillit, H. M., Damle, S., Mahabir, R., Kefalides, N. A., Gregory, J. D., Antonovych, T., Sabnis, S., and Zabriskie, J. B.: Monoclonal antibodies to heparan sulfate proteoglycan. Development and application to the study of normal tissue and pathologic human kidney biopsies. Connect. Tissue Res. 18:9, 1988.

26. Carbonetto, S.: The extracellular matrix of the nervous systems. Trends Neurosci. 7:382, 1984.

27. Ruoslahti, E., and Yamaguchi, Y.: Proteoglycans as modulators of growth factor activities. Cell 64:867, 1991.

28. Scott, J. E., and Orford, C. R.: Dermatan sulphate-rich proteoglycan associates with rat tail-tendon collagen at the d band in the gap region. Biochem. J. 197:213, 1981.

29. Knepper, P. A., Hvizd, M. G., McLone, D. G., Higbee, R. G., Goossens, W., and Palmberg, P. F.: GAG profile of normal and POAG lamina cribrosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 564.

30. Fukuchi, T., Sawaguchi, S., Yue, B., Iwata, K., Hara, H., Shirakashi, M., and Kaiya, T.: Sulfated proteoglycans of the optic nerve head in normal and in laser-induced glaucomatous monkey eyes. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 874.

31. Loewi, G., and Meyer, K.: The acid mucopolysaccharides of embryonic skin. Biochim. Biophys. Acta 27:456, 1958.

32. Gregory, J. D., Damle, S. P., Covington, H. I., and Cintron, C.: Developmental changes in proteoglycans of rabbit corneal stroma. Invest. Ophthalmol. Vis. Sci. 29:1413, 1988.

33. Kublin, C. L., and Cintron, C.: Glycosaminoglycans in healthy rabbit corneas. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 1163.

A 20-Year Series of Orbital Exenteration

Peter S. Levin, M.D., and Jonathan J. Dutton, M.D.

We reviewed patient records of 99 consecutive orbital exenterations performed between 1969 and 1988. Patients ranged in age from 2 to 86 years (mean, 55.9 years). Classification of cases on histopathologic criteria showed 32 exenterations were performed for squamous cell carcinoma originating in the paranasal sinus (13), skin (12), conjunctiva (six), and lacrimal sac (one). Orbital exenteration was performed for treatment of other epithelial malignancy in basal cell carcinoma (eight), sebaceous carcinoma (six), adenoid cystic carcinoma (five), undifferentiated carcinoma (four), adenocarcinoma (two), intraepithelial carcinoma of the conjunctiva (two), benign mixed tumor (one), and transitional cell carcinoma (one). Exenterations were performed for melanoma of the conjunctiva (ten), nasosinus (three), skin (two), orbit (two), and choroid (one). Exenterations were also performed as treatment for mucormycosis (five), meningioma (three), fibrosarcoma (two), rhabdomyosarcoma (two), hemangiopericytoma (two), orbital cellulitis (one), fibrous histiocytoma (one), schwannoma (one), lymphangioma (one), benign lymphoepithelial lesion (one), and undifferentiated malignancy (one).

ORBITAL EXENTERATION entails removal of the eye together with its extraocular muscles and other soft tissues of the orbit. The procedure is usually performed with reluctance because it generally represents the failure of alternative treatments.

We reviewed conditions leading to orbital exenteration in 99 patients at our institution between 1969 and 1988.

Patients and Methods

Since 1969, a computerized database of surgical procedures and discharge diagnoses has been maintained at our institution. A database search of the years 1969 to 1989 disclosed 93 cases of orbital exenteration. A search of files in the eye pathology laboratory yielded an additional six cases. This study would not have identified cases that were not entered into the medical records system or found in eye pathology files. All patient charts were examined to determine the initial clinical features and diagnoses. Follow-up was inconsistent because some patients underwent operations at our institution but received postoperative care at other facilities and were, therefore, lost to our follow-up. In several cases, a death certificate was available, but did not specify whether death was tumor-related.

Results

We identified 99 cases (60 males and 39 females) of orbital exenteration. Patients ranged in age from 2 to 86 years (mean, 55.9 years).

The indications for an operation were as follows: (1) treatment of life-threatening neoplasm in 88 (89%), (2) treatment of life-threatening infection in six (6%), and (3) treatment of pain or deformity in five (5%).

Cases were also classified on confirmed histopathologic criteria as epithelial neoplasms (61), melanoma (18), infectious processes (six), mesenchymal tumors (five), nerve-sheath tumors (four), vascular lesions (three), lymphoproliferative disorders (one), or undifferentiated malignancy (one).

Thirty-two of the 61 epithelial neoplasms were exenterated as part of the treatment for squamous carcinoma originating in the paranasal sinus, conjunctiva, skin, or lacrimal sac. In the 13 patients with squamous cell carcinoma

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originating in the paranasal sinus, combined orbital and sinus exenteration was performed. Seven of these patients died from several days to 2½ years after exenteration (median, nine months). Three survivors were disease-free at 2½, seven, and 14 years after exenteration. Three patients were lost to follow-up examination.

Six conjunctival squamous cell lesions initially were manifest three months to five years (median, 1½ years) before exenteration. Three patients died at eight months, two years, and three years after exenteration, whereas three others were free of recurrence at two, three, and six years after the operation.

In 12 patients, squamous cell carcinoma originated from a cutaneous site and extended to the orbit. Four patients had initial eyelid involvement and eight others had initial involvement of the cheek, brow, nose, temple, forehead, or multiple periorbital sites. Six known fatalities occurred at one to five years (median, two years) after exenteration. The other six patients were alive at one month to seven years (median, 4½ months) after the operation.

One patient had a squamous cell carcinoma of the lacrimal sac. He died ten years after the operation from cerebrovascular disease.

In eight patients, exenteration was performed for orbital extension of eyelid basal cell carcinoma. Five of these patients had initial lesions in the medial canthus. Six patients had previously undergone an operation or radiotherapy. The basal cell nevus syndrome was diagnosed in one patient. Five patients showed no recurrence at 12 months. In one patient, tumor recurred within one year. Two patients were lost to follow-up. Six patients aged 26 to 62 years (median, 58 years) had sebaceous carcinoma. In five patients, eyelid abnormalities had been present for two to 12 years (median, four years) before exenteration. Four patients died at 1½ to five years after exenteration (median, three years). A fifth patient was alive and well two years postoperatively. No clinical information is available on the 26-year-old patient.

Orbital exenteration was performed for 15 other cases of epithelial malignancy. Exenteration was performed for adenoid cystic carcinoma (five), undifferentiated carcinoma (four), adenocarcinoma (two), intraepithelial carcinoma of the conjunctiva (two), benign mixed tumor of the lacrimal gland (one), and transitional cell carcinoma of the lacrimal sac (one).

Orbital exenteration was performed for melanomas of the conjunctiva (ten), nasal sinus (three), orbit (two), choroid with extrascleral extension (one), skin (one), and nevus of Ota with cutaneous malignancy (one). Clinical histories were available in nine of the ten cases of conjunctival melanoma. Abnormal conjunctival pigmentation had been present for two months to 12 years (median, six years) before exenteration. Three patients were alive and well one, two, and 12 years after exenteration. Six patients died two months to ten years after exenteration (median, 1½ years).

Exenterations were also performed as treatment for infection in six patients. All five patients with mucormycosis had diabetes mellitus, and three patients had diabetic ketoacidosis at initial examination. Two of these patients died in the perioperative period. In one patient without evidence of zygomycosis, orbital exenteration was performed in the presence of pansinusitis, panophthalmitis, and central retinal vein occlusion. Acute orbital inflammation and necrosis but no organism was found on laboratory study.

Three patients with meningiomas and one patient with an orbital schwannoma progressed to exenteration. All of these patients had progressive proptosis with corneal exposure and compromise. Two cases were of sphenoid wing meningiomas diagnosed 13 and 14 years before extensive orbital extension warranted orbital exenteration. One case was of an orbital meningioma of four years' duration. The patient with the schwannoma had had proptosis for 37 years before orbital exenteration. All patients did well except for one of the patients with a sphenoid wing meningioma who had partial excision of a nasal tumor four years after orbital exenteration and was doing poorly nine years after orbital exenteration.

Mesenchymal tumors accounted for five orbital exenterations. Two patients had rhabdomyosarcoma. Chemotherapy and radiation therapy had failed for one patient and the patient died within one year. The other patient received exenteration succeeded by chemotherapy and radiation therapy and was alive 13 years later. Two patients had fibrosarcoma; one had had a previous history of retinoblastoma treated with radiation therapy. Both patients died within two years of exenteration. A patient with an aggressive orbitosinus fibrous histiocytoma was alive and well ten years later.

Of three vascular lesions accounting for exenteration, two were hemangiopericytomas. An 18-year-old patient died four months after exenteration. A 26-year-old patient who had shown rapid progression of an orbitosinus hemangiopericytoma was alive and well 15 years later. One patient received exenteration as treatment for orbital lymphangioma that had caused severe recurrent orbital bleeding, pain, and a visual acuity of hand motion.

One patient received orbital exenteration because of a lacrimal fossa mass that pathologic examination disclosed as a benign lymphoepithelial lesion (Mikulicz's syndrome). No follow-up was available.

One patient had an undifferentiated neoplasm of the maxillary sinus with carcinomatous and sarcomatous elements. This patient was alive and well 14 years later.

Four of the 99 patients previously described on the basis of histopathologic criteria had clinically evident lacrimal gland fossa tumors. Two patients had exenteration for adenoid cystic carcinoma. One of these had had eight months of proptosis at the time of initial examination. A recurrence two years later was treated with radiation, and an additional recurrence with lung metastases six years later was treated with chemotherapy. This patient died from the disease 11 years after orbital exenteration. A second patient with a four-week history of orbital disease died of regional and metastatic disease one year after the operation. The one patient with benign mixed tumor of the lacrimal gland had had an incomplete excision with rupture of the pseudocapsule of the tumor 23 years earlier. She had severe proptosis at initial examination and was alive and well 17 years after orbital exenteration. The fourth lacrimal gland fossa mass was in the patient with the benign lymphoepithelial lesion.

Discussion

Orbital exenteration causes blindness and deformity. This study shows the following three indications for orbital exenteration performed from 1969 to 1988: (1) eradication of presumed life-threatening malignancy, 89%; (2) eradication of presumed life-threatening infection, 6%; and (3) alleviation of intractable pain or deformity, 5%.

Our study is consistent with other large studies[1-5] that showed that orbital exenteration is most frequently performed for the treatment of life-threatening malignancy. Orbital exenteration was performed for presumed life-threatening epithelial neoplasm in 61 patients. Our experience was similar to that of other investigators in showing the predominance of epithelial malignancy as the indication for exenteration (Table).

Seven of eight exenterations performed for basal cell carcinoma in our study were performed for recurrent lesions. This is consistent with other reports suggesting that recurrent basal cell carcinomas have a greater chance of recurring than do primary tumors.[6,7] Although published studies report that only 10% to 24% of periocular basal cell carcinomas develop at the medial canthus,[8] three of eight basal cell carcinomas ultimately requiring exenteration at our institution originated in the medial canthus and five of eight exenteration specimens had medial orbital involvement on histopathologic examination. This high recurrence rate for medial canthal basal cell carcinomas has been reported.[7] Adequate treatment of the medial canthus is difficult because of the extensive vessels and nerves that extend from the medial canthus back into the orbit and the presence of the nasolacrimal drainage system. Current guidelines for excision of medial canthal basal cell carcinoma[9,10] were confirmed by the experience at our institution. Medial canthal tumors may spread into the orbit and, therefore, medial canthal basal cell carcinomas warrant the most effective primary modalities of treatment.

Secondary orbital involvement from paranasal sinus malignancy has been estimated to be 60%.[11,12] In our study, squamous cell carcinoma of the paranasal sinuses accounted for 12 orbital exenterations and sinus melanoma accounted for another three. In three of these cases, final pathologic reports indicated no orbital invasion by tumor, which emphasizes that orbital involvement may be difficult to assess. The indications for orbital exenteration because of neoplasm of the paranasal sinuses may diminish as surgeons supplement clinical observations with the high-resolution orbital and sinus imaging techniques currently available.

Our experience with lacrimal gland fossa tumors is consistent with the reported literature. Only one patient with adenoid cystic carcinoma of the lacrimal gland is reported to be alive and well without recurrent tumor 20 years after the operation.[13] Our experience with two patients is consistent with this poor prognosis. Although one of our patients lived for 11 years after exenteration, she had recurrent disease within two years of exenteration and had metastatic disease six years after the operation. The case of

TABLE
A COMPARISON OF ORBITAL EXENTERATION AT SIX INSTITUTIONS*

	WILMER INSTITUTE	UNIVERSITY OF CALIFORNIA AT SAN FRANCISCO	UNIVERSITY OF KANSAS	MAYO CLINIC	UNIVERSITY OF NAPLES	DUKE UNIVERSITY
	1927–1953	1940–1971	1951–1964	1967–1986	1976–1986	1969–1988
	(N = 48)	(N = 48)	(N = 31)	(N = 102)	(N = 39)	(N = 99)
Squamous cell carcinoma	4	6	3	33	7	32
Skin	3	2	1	NA†	6	12
Sinus	1	0	2	NA	1	13
Conjunctiva	0	3	0	NA	0	6
Tear sac	0	1	0	NA	0	1
Basal cell carcinoma	11	14	11	21	9	8
Sebaceous carcinoma	0	1	0	6	0	6
Other epithelial tumors	6	8	5	9	10	15
Malignant melanoma	12	8	7	16	8	18
Conjunctiva	3	5	NA	NA	1	10
Sinus	0	0	NA	NA	0	3
Choroid	9	2	NA	8	7	1
Other	0	1	NA	NA	0	4
Rhabdomyosarcoma	2	5	2	2	2	2
Infectious	1	0	0	1	0	6
Other	12	6	3	14	3	12

*At Wilmer, University of California at San Francisco, and University of Naples only, exenterations performed by ophthalmology departments were surveyed; at University of Kansas, Mayo Clinic, and Duke University, all exenterations were reported, regardless of the department performing the operation.

†NA indicates no data available.

our patient with benign mixed tumor of the lacrimal gland leading to exenteration attests to the recurrence of locally aggressive, but histopathologically benign tumor when subtotal initial excision is performed.[14]

Current treatment trends have diminished the life-preserving role of orbital exenteration in certain specific neoplastic diseases. In our study, exenteration was performed in ten patients with conjunctival melanomas who had preexisting pigmentary abnormality for up to 12 years. With the success of earlier aggressive excision and cryotherapy of affected conjunctival tissues, orbital exenteration is now reserved for cases of deep orbital involvement.[15] Previously, exenteration was the accepted primary treatment for orbital rhabdomyosarcoma. In the three published studies ending before 1971,[3-5] nine of the 127 orbital exenterations were for rhabdomyosarcoma, whereas in the three studies (including ours) from 1967 to 1989,[1,2] rhabdomyosarcoma accounted for six of 239. In our study, only two exenterations were performed for rhabdomyosarcoma and one of these represented the failure of previous nonsurgical therapy. Today, exenteration for rhabdomyosarcoma is reserved for tumors unresponsive to other therapies.[16] Orbital exenteration does not affect the ultimate prognosis for life in cases of extrascleral extension of intraocular melanoma.[17-19] Local resection of melanoma and adjacent Tenon capsule is the treatment of choice for extrascleral extension of choroidal melanoma. Local conjunctival excision may be preferable to exenteration in the management of superficial squamous cell carcinoma of the conjunctiva without demonstrable orbital involvement.[20]

The second category of disease leading to orbital exenteration in our study was life-threatening infection with mucormycosis leading to five exenterations and orbital cellulitis leading to one exenteration. Rhino-orbital phycomycosis including cases from our institution has previously been reviewed.[21,22] Although orbital exenteration is consistent with the treatment principles of wide debridement of involved tissues, effective treatment of selected patients can be provided without a radical operation.[23,24]

Severe deformity and disability led to orbital exenteration in five patients (5%). Three patients had progressive meningioma with blindness, proptosis, and exposure keratopathy. One had a schwannoma with marked proptosis and corneal ulceration. The fifth patient had a lymphangioma of the orbit with a visual acuity of hand motion and painful hemorrhages that required recurrent hospitalization. Although not life-prolonging, these procedures were indicated because of severe deformity or pain. Although orbital exenteration remains a viable alternative in such patients, some of them can be treated effectively today with combined intracranial and orbital operations[25] to excise intraorbital tumor without sacrificing the eye, and with improved cosmesis.

Other conditions that are not life-threatening but which may lead to exenteration are severe orbital contracture,[26] severe unremitting orbital inflammatory processes,[2] and neurofibromatosis with orbital deformity and visual loss.[27]

An improved spectrum of reconstructive and prosthetic options is now available that makes orbital exenteration a more acceptable procedure than it was in the past.[28] Local reconstructive techniques, primarily split-thickness skin grafting and healing by granulation, result in rapid rehabilitation and allow detection of recurrent disease. Regional reconstructive techniques, such as temporalis muscle transfer procedures[29-31] and galeofrontalis fascial flaps,[32] as well as distant reconstructive techniques, such as free latissimus dorsi myocutaneous free flaps,[33] allow for partial or total obliteration of the exenteration cavity and may provide considerable benefits for the patient who has undergone orbital exenteration. Such reconstructive options may be more acceptable to patients who require exenteration for control of disease.

References

1. Bartley, G. B., Garrity, J. A., Waller, R. R., Henderson, J. W., and Ilstrup, D.M.: Orbital exenteration at the Mayo Clinic. 1967–1986. Ophthalmology 96:468, 1989.

2. de Conciliis, C., and Bonavolontà, G.: Incidence and treatment of dural exposure and CSF leak during orbital exenteration. Ophthalmic Plast. Reconstr. Surg. 3:61, 1987.

3. Naquin, H. A.: Exenteration of the orbit. Arch. Ophthalmol. 51:850, 1954.

4. Rathbun, J. E., Beard, C., and Quickert, M. H.: Evaluation of 48 cases of orbital exenteration. Am. J. Ophthalmol. 72:191, 1971.

5. Simons, J. N., Robinson, D. W., and Masters, F. W.: Malignant tumors of the orbit and periorbital structures treated by exenteration. Plast. Reconstr. Surg. 37:100, 1966.

6. Menn, H., Robins, P., Kopt, A. W., and Bart, R. S.: The recurrent basal cell carcinoma. Arch. Dermatol. 103:628, 1971.

7. Robins, P., Rodriguez-Sains, R., Rabinovitz, H., and Rigel, D.: Mohs surgery for periocular basal cell carcinomas. J. Dermatol. Surg. Oncol. 11:1203, 1985.

8. Henkind, P., and Friedman, A.: Cancer of the lids and ocular adnexa. In Andrade, R., Gumport, S. L., Popkin, G. L., and Reese, R. D. (eds.): Cancer of the Skin, vol. 2. Philadelphia, W. B. Saunders Company, 1976, p. 1351.

9. Doxanas, M. T., Green, W. R., and Iliff, C. E.: Factors in the successful surgical management of basal cell carcinoma of the eyelids. Am. J. Ophthalmol. 91:726, 1981.

10. Mohs, F. E.: Micrographic surgery for the microscopically controlled excision of eyelid cancers. Arch. Ophthalmol. 104:901, 1986.

11. Johnson, L. N., Krohel, G. B., Yeon, E. B., and Parnes, S. M.: Sinus tumors invading the orbit. Ophthalmology 91:209, 1984.

12. Conley, J., and Baker, D. C.: Management of the eye socket in cancer of the paranasal sinuses. Arch. Otolaryngol. 105:702, 1979.

13. Henderson, J. W.: Adenoid cystic carcinoma of the lacrimal gland, is there a cure? Trans. Am. Ophthalmol. Soc. 85:312, 1987.

14. Wright, J. E., Stewart, W. B., and Krohel, G. B.: Clinical presentation and management of lacrimal gland tumors. Br. J. Ophthalmol. 63:600, 1979.

15. Jakobiec, F. A., Brownstein, S., Albert, W., Schwarz, F., and Anderson, R.: The role of cryotherapy in the management of conjunctival melanoma. Ophthalmology 89:502, 1982.

16. Wharam, M., Beltangady, M., Hays, D., Heyn, R., Ragab, A., Soule, E., Tefft, M., and Maurer, H.: Localized orbital rhabdomyosarcoma. Ophthalmology 94:251, 1987.

17. Kersten, R. C., Tse, D. T., Anderson, R. L., and Blodi, F. C.: The role of orbital exenteration in choroidal melanoma with extrascleral extension. Ophthalmology 92:436, 1985.

18. Pach, J. M., Robertson, D. M., Taney, B. S., Martin, J. A., Cambell, R. J., and O'Brien, P. C.: Prognostic factors in choroidal and ciliary body melanomas with extrascleral extension. Am. J. Ophthalmol. 101:325, 1986.

19. Rini, F. J., Jakobiec, F. A., Hornblass, A., Beckerman, B. L., and Anderson, R. L.: The treatment of advanced choroidal melanoma with massive orbital extension. Am. J. Ophthalmol. 104:634, 1987.

20. Iliff, W. J., Marback, R., and Green, W. R.: Invasive squamous cell carcinoma of the conjunctiva. Arch. Ophthalmol. 93:119, 1975.

21. Schwartz, J. N., Donnelly, E. H., and Klintworth, G. K.: Ocular and orbital phycomycosis. Surv. Ophthalmol. 22:3, 1977.

22. Gamba, J. L., Woodruff, W. W., Djang, W. T., and Yeates, A. E.: Craniofacial mucormycosis. Assessment with CT. Radiology 160:207, 1986.

23. Kohn, R., and Hepler, R.: Management of limited rhino-orbital mucormycosis without exenteration. Ophthalmology 92:1440, 1985.

24. Lee, H. W., and Liao, H. R.: Treatment of rhino-orbital mucormycosis without exenteration. Trans. Ophthalmol. Soc. Repub. China 26:585, 1987.

25. Maroon, J. C., and Kennerdell, J. S.: Surgical approaches to the orbit. Indications and techniques. J. Neurosurg. 60:1226, 1984.

26. Small, R. G., and LaFuente, H.: Exenteration of the orbit in selected cases of several orbital contracture. Ophthalmology 90:236, 1983.

27. Jackson, I. T., Laws, E. R., Jr., and Martin, R. D.: The surgical management of orbital neurofibromatosis. Plast. Reconstr. Surg. 71:751, 1983.

28. Levin, P. S., Ellis, D. S., Stewart, W. B., and Toth, B. A.: Orbital exenteration. The reconstructive ladder. Ophthalmic Plast. Reconstr. Surg. 7:84, 1991.

29. Holmes, A. D., and Marshall, K. A.: Uses of the temporalis muscle flap in blanking out the orbits. Plast. Reconstr. Surg. 63:336, 1979.

30. Naquin, H. A.: Orbital reconstruction. Utilizing temporalis muscle. Am. J. Ophthalmol. 41:519, 1956.

31. Shagets, F. W., Panje, W. R., and Shore, J. W.: Use of temporalis muscle flaps in complicated defects of the head and face. Arch. Otolaryngol. Head Neck Surg. 112:60, 1986.

32. Brent, B., Upton, J., Acland, R. D., Shaw, W. W., Finseth, F. J., Rogers, C., Pearl, R. M., and Hentz, V. R.: Experience with the temporoparietal fascial flap. Plast. Reconstr. Surg. 76:177, 1985.

33. Donahue, P. J., Liston, S. L., Falconer, D. P., and Manlove, J. C.: Reconstruction of orbital exenteration cavities. The use of the latissimus dorsi myocutaneous free flap. Arch. Ophthalmol. 107:1681, 1989.

OPHTHALMIC MINIATURE

He was a touch nearsighted, and the mesh of the window screen seemed more distinct to him than what lay beyond it. What lay beyond it—home—had the blocky, blurred appearance of something worked in needlepoint, each tiny square in the screen filled with a square of color. Not only was there a needlepoint house but also a needlepoint car out front, a needlepoint swing on the porch, a needlepoint bicycle in the yard.

Anne Tyler, *Saint Maybe*
New York, Alfred A. Knopf, 1991, p. 182

Problems Associated With Conjunctivodacryocystorhinostomy

G. Chandra Sekhar, M.D., Richard K. Dortzbach, M.D., Russell S. Gonnering, M.D., and Bradley N. Lemke, M.D.

Fifty-eight patients (69 eyes) underwent conjunctivodacryocystorhinostomy for lacrimal canalicular obstruction. The cause of lacrimal obstruction and the results and complications of the operation were analyzed. Trauma and idiopathic disease were the most common causes of lacrimal canalicular obstruction in 24 of 69 (34.8%) eyes each. Relief of epiphora was achieved in 68 of the 69 eyes (98.5%). The complications included tube displacement in 40 of the 69 eyes (57.9%), tube obstruction in 19 of the 69 eyes (27.5%), and infection of the lacrimal sac in four of the 69 eyes (5.8%). Despite frequent complications, most Jones tubes can be made to function satisfactorily. Conjunctivodacryocystorhinostomy remains the best surgical treatment at this time for permanent loss of canalicular function.

OBSTRUCTION of the lacrimal drainage system temporal to the common internal punctum of the canaliculi can be caused by trauma, drugs, viral infections, operations for tumors at the medial canthus, and congenital agenesis.[1,2]

Conjunctivodacryocystorhinostomy with a Jones Pyrex glass tube (Gunther Weiss, Scientific Glass Blowing Co., Beaverton, Oregon) is the standard treatment in these situations.[3] Maintenance of the anatomic position and the function of the tube is difficult.[1,4] A number of modifications of the operation or tube style have had varying success.[5-9]

The results and complications of conjunctivodacryocystorhinostomy performed over a 17-year period from 1973 to 1989 from the practices of three of us (R.K.D., B.N.L., R.S.G.) were analyzed. Only those patients who had at least six months of follow-up after the operation were included in the study. We studied the cause of lacrimal canalicular occlusion and the results and complications of conjunctivodacryocystorhinostomy in 69 eyes of 58 patients.

Subjects and Methods

Of the 58 patients who were the subjects of this study, 28 were male and 30 were female. Their ages ranged from 2 to 90 years with a mean of 41.5 years. The lacrimal obstruction was bilateral in 11 patients, giving a total of 69 eyes in the 58 patients.

Causes of Lacrimal Occlusion

The causes of lacrimal drainage abnormalities were analyzed (Table 1). Trauma leading to canalicular obstruction was caused by either a motor vehicle accident or an animal bite. Drugs that led to canalicular obstruction were 5-fluorouracil in two cases and idoxuridine in one

TABLE 1
CAUSES OF LACRIMAL CANALICULAR OBSTRUCTION IN 69 EYES

CAUSE	NO. OF EYES (%)
Trauma	24 (34.8)
Idiopathic	24 (34.8)
Congenital agenesis	8 (11.6)
Tumor	5 (7.3)
Drugs and viral infections	5 (7.3)
Conjunctival inflammation	2 (2.9)
Pump failure	1 (1.4)

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case. Viral infections comprised herpes zoster in one patient and herpes simplex in two patients (idoxuridine used in one of them).

Surgical Technique for Conjunctivodacryocystorhinostomy

Anesthesia for adults entailed local anesthesia with intravenous sedation. Local anesthesia was accomplished with 1% lidocaine with epinephrine 1:100,000 injected in the medial canthus, in an anterior ethmoidal nerve block, and in the middle meatus of the nose. The nose was packed with ribbon gauze containing 4% cocaine solution. Children received a general anesthetic and similar injections (except the anterior ethmoidal nerve block), and the cocaine nasal pack was used to provide hemostasis.

The operative area was prepared with povidone-iodine and draped. After a skin incision and exposure of the bone along the medial wall of the lacrimal sac fossa were accomplished, a bony ostium was created with Kerrison rongeurs. The bony ostium was initiated by one of us (R.S.G.) in some cases with a diamond burr. The ostium measured about 2 × 1.5 cm. Anteriorly hinged flaps were created in the lacrimal sac and nasal mucosa. A portion of the caruncle was then excised. The nasal pack was removed and a Wheeler knife was used to make a tract in the medial canthus from the caruncle to the nose. A Bowman probe was introduced into the tract to identify it, and the tract was then enlarged with scissors or a trocar.

The length of the Jones Pyrex tube to be used was measured. A second lacrimal probe was passed down the tract until it touched the septum. This second probe was grasped with a forceps at the medial canthal angle and then removed. The distance from the forceps to the end of the probe represented the distance from the medial canthal angle to the septum. It was estimated that this length minus 2 mm was the approximate desired length of the Jones tube, which would allow the nasal end of the tube to be suspended in the middle of the nostril. The Jones tube, usually with a 3.5- or 4.0-mm flange, was then introduced into the tract. The tube was placed so that the nasal end was about 2 mm lateral to the nasal septum, approximately in the middle of the nostril. To achieve this ideal placement of the tube, long Jones tubes (19 to 27 mm) or flanged silicone tubes were required in some patients. Jones tubes were held in place with a 6-0 Prolene suture passed through a hole in the flange and attached to adjacent medial canthal tissues. When using flanged silicone tubes, the surgeon should place the suture through the silicone flange instead of a specific hole. Once the medial canthal tissues healed around the initial tube, this tube could be replaced with a second tube with a smaller flange (3.0 mm), if necessary.

Results

Incidence and Management of Complications

Follow-up data were analyzed (Table 2). At the last follow-up contact with the patients, 57 of the 58 patients (68 of the 69 eyes) were free of epiphora. In the patients with tubes in place, patency was confirmed with free irrigation into the nose, a positive sniff test (air flowing through the tube when the patient sniffed), or fluorescein dye disappearance. Of the 68 eyes free of epiphora, 63 had Jones tubes, one had a flanged silicone tube, and four had no tube because of tube extrusion. The duration of the period with the Jones tube in place and the duration of the epiphora-free period after extrusion of the Jones tube in these latter four

TABLE 2

FOLLOW-UP DATA OF CONJUNCTIVODACRYOCYSTORHINOSTOMY PERFORMED ON 69 EYES

		TEARING	
DURATION OF FOLLOW-UP (YRS)	NO. OF EYES	NO. WITHOUT TEARING	NO. WITH TEARING
0.5–1	15	14	1
1.0–3	24	24	0
4.0–5	11	11	0
6.0–10	16	16	0
> 10	3	3	0
Total	69	68	1

TABLE 3
LACK OF TEARING AFTER EXTRUSION OF JONES TUBE

CASE NO.	DURATION OF PERIOD WITH JONES TUBE IN PLACE (YRS)	DURATION OF PERIOD WITHOUT TEARING AFTER EXTRUSION (YRS)*
1	4.0	3.0
2	2.5	6.0
3	6.0	9.0
4	7.0	4.5

*No tearing observed at last time of contact with patient.

patients were determined (Table 3). The only patient who had symptomatic tearing had narrow nares, could not retain any of the three tubes replaced, and refused a corrective operation for nasal septal deviation to widen the nares. Various complications and their incidence were studied (Table 4).

Displacements—Displacement of the tube from the intended position in the medial canthus, causing epiphora, developed in 40 eyes (Table 4). In all tube replacement procedures, a nasal examination was performed to ascertain proper placement of the tube in the nostril.

Extrusion—Extrusion means total displacement of the tube from its intended position. Sometimes the patients brought in the tube, and sometimes they were not aware when the tube was lost. If the patient reported soon after the extrusion and the tract of the tube was visible, tube replacement was performed as an office procedure with the patient under topical or local anesthesia, or both. However, if the tract was obliterated, local anesthesia with intravenous sedation or general anesthesia was necessary. A new tract was created and the tube was inserted. Often it was noticed that the length of the tube used at the primary procedure varied from the length of the tube needed for replacement.

Medial displacement—Clinical differentiation between medial migration and extrusion was difficult in some patients because the tube was not visible or palpable in the medial canthus. With medial migration, the tube may be recognized only on exploration or visualization of the medial end of the tube in the nose. In this situation, the tube was identified, brought up to the medial canthal area, and reattached to medial canthal tissues with a 6-0 Prolene suture. Usually, a longer tube had to be used in these cases.

Lateral displacement—This complication was usually caused by narrow nares or a tube that was too long and required replacement of the tube with one of appropriate size. In two patients the nares were narrow; one of them underwent a corrective rhinologic procedure, and the other refused further treatment.

The timing of the tube displacements was analyzed. Twelve of the 19 tube extrusions, seven of the nine medial migrations, and eight of the 12 lateral displacements occurred in the first three months after the operation. Thus, of the total 40 tube displacements, 27 (67.5%) happened in the first three months. Of these 40 displacements, replacement with a different tube was required in 18 eyes, and repositioning of the same tube was carried out in the remaining eyes. The tube replacement was necessary once in ten eyes, twice in seven eyes, and three times in one eye. Twenty-seven tube replace-

TABLE 4
COMPLICATIONS OF CONJUNCTIVODACRYOCYSTORHINOSTOMY PERFORMED ON 69 EYES

COMPLICATIONS	NO. OF EYES (%)
Displacement of tube	
Extrusions	19 (27.5)
Medial displacement	9 (4.3)
Lateral displacement	12 (17.4)
Total	40 (57.9)
Obstruction of tube	
Nasal (cicatrix, mucosa)	9 (13.0)
Conjunctival granuloma	5 (7.3)
Conjunctival overgrowth	5 (7.3)
Total	19 (27.5)
Others	
Infection	4 (5.8)

ment procedures were performed. A flanged silicone tube was used in 16 eyes (in four eyes during the primary conjunctivodacryocystorhinostomy and in 12 eyes for the replacement of the Jones tube during the follow-up).

Obstruction—Obstruction of the tube with mucus, which was relieved by irrigation or probing, is considered routine in the use of Jones tubes and is not included in our complications. Nasal obstruction caused by growth of cicatrix or nasal mucosa over the nasal end of the tube, or both, was corrected by creation of a new tract and replacement of the tube or by excision of the offending tissues in the nose. Obstruction at the canthus was treated by excision of the causative granuloma or conjunctival overgrowth.

Infection—Infection was manifested by chronic regurgitation of purulent material from the puncta in three patients and by acute infection in the lacrimal sac area in the fourth patient. In three of these patients (two with regurgitation of purulent material from the puncta and one with acute sac infection), the infection resolved completely on conservative treatment with topically applied, instilled, and systemic antibiotics. In the fourth patient, surgical exploration was performed and the sealed-off sac was reanastomosed with the nasal mucosa after enlarging the bony ostium.

Discussion

Conjunctivodacryocystorhinostomy was described in 1962 by Jones[3] as a conduit between the lacrimal lake and the nose for cases of lacrimal canalicular obstruction. The procedure subsequently has been modified by Jones and others.[5-9] The number of modifications that have been put forth indicates that the ideal treatment for obstructed lacrimal canaliculi is yet to be determined.

A number of etiologic factors for canalicular obstruction have been described.[1,2] Trauma and idiopathic disease were the most common causes in our study (24 eyes [34.8%] each). Motor vehicle accidents and animal bites were the two predominant types of injury. Because of associated systemic injuries, eyelid and lacrimal trauma may be overlooked. Careful examination immediately after trauma and early primary management of canalicular injury help to prevent subsequent obstruction of the canaliculi. In the future, a better understanding of the pathogenesis in the idiopathic group may lead to prevention of canalicular obstruction and reduce the need for conjunctivodacryocystorhinostomy.

Congenital agenesis of the lacrimal drainage system may involve the puncta, the canaliculi, along with other parts of the drainage system, or any of these areas. The extent of agenesis often is difficult to judge clinically. If the canaliculi are involved, conjunctivodacryocystorhinostomy is necessary to eliminate tearing.

Relief of epiphora was achieved in 68 of 69 (98.5%) eyes in this study. Despite this high rate of success, extensive care was required to maintain the anatomic position and the function of the tube. Medial or lateral tube displacement or total extrusion was seen in 40 of 69 (57.9%) eyes, 27 of these 40 tube displacements or extrusions (67.5%) occurring within the first three months after the operation. The flange at the lateral end of the tube and the flared nasal end help to prevent displacement once firm cicatrix develops around the tube in the postoperative period. However, displacement may still occur at any time. This was confirmed in our study, as 32.5% of the displacements took place after the first three months and extrusion occurred as late as seven years after the operation in one patient (Case 4; Table 3). A firm cicatrix probably never forms around the tube in some patients.

Twenty-seven tube replacements were performed in 18 eyes. These included replacement with a Jones tube or a flanged silicone tube. The length of the tube measured during the primary procedure may not be ideal later because of edema during the operation and subsequent scarring and contracture of these tissues. Improper length of the tube is a major cause for the displacement of a Jones tube. A long tube may cause lateral displacement, and a short tube may result in medial or nasal migration.

A flanged silicone tube was used in place of a Jones tube in 16 eyes. This was required because none of the Jones tubes used could be ideally placed in the nose. All but one of these tubes were later exchanged for a Jones tube at various postoperative periods when the patients had epiphora. Flanged silicone tubes have poor capillarity and do not drain as well as Jones Pyrex tubes. However, they may provide some drainage and are useful in maintaining a tract until complete healing has developed. At that time, a Jones tube can be placed and stay in satisfactory position. Surgeons contemplating conjunctivodacryocystorhinostomy should have an adequate inventory of Jones tubes and flanged silicone tubes to be prepared for all situations.

Four patients were free of epiphora over a period of three to nine years after extrusion of the Jones tube without replacement. These patients had had a Jones tube for a period ranging from 2.5 to seven years. Although this situation was described earlier,[10] the response of tissues in the absence of a Jones tube varies and most often the tract tends to close.[9] Therefore, it is probably wise to leave the tube in place indefinitely.

Infection of the lacrimal sac area was seen in four patients. The clinical findings of chronic mucopurulent reflux from the puncta in three patients and acute infection in the fourth patient probably resulted from part of the sac being walled off. Tears draining around the outside of the tube can thereby be retained and become infected. This emphasizes the need for an adequate osteotomy and good flaps even if the entire lacrimal drainage system is bypassed with a Jones tube.

Our experience clearly highlights the beneficial role of a Jones tube in conjunction with conjunctivodacryocystorhinostomy in the treatment of lacrimal canalicular obstruction. Although there is a high incidence of complications, conjunctivodacryocystorhinostomy is currently the best way to treat permanent loss of canalicular function. With good patient motivation and attentive postoperative care, most Jones tubes can be made to function satisfactorily.

References

1. Lamping, K., and Levine, M. R.: Jones tubes. How good are they? Arch. Ophthalmol. 101:260, 1983.
2. Steinsapir, K. D., Glatt, H. J., and Putterman, A. M.: A 16-year study of conjunctival dacryocystorhinostomy. Am. J. Ophthalmol. 109:387, 1990.
3. Jones, L. T.: The cure of epiphora due to canalicular disorders, trauma and surgical failures on the lacrimal passages. Trans. Am. Acad. Ophthalmol. Otolaryngol. 66:506, 1962.
4. Nagashima, K.: Rocking phenomenon of Jones' tube in place. Its clinical importance. Arch. Ophthalmol. 102:116, 1984.
5. Jones, L. T.: Conjunctivodacryocystorhinostomy. Am. J. Ophthalmol. 59:773, 1965.
6. Soll, D. B.: Vein grafting in nasolacrimal system reconstruction. Ophthalmic Surg. 14:656, 1983.
7. Campbell, C. B., III, Shannon, G. M., and Flanagan, J. C.: Conjunctivodacryocystorhinostomy with mucous membrane graft. Ophthalmic Surg. 14:647, 1983.
8. Gladstone, G. F., and Putterman, A. M.: A modified glass tube for conjunctivodacryocystorhinostomy. Arch. Ophthalmol. 103:1229, 1985.
9. Henderson, P. N.: A modified trephining technique for the insertion of Jones tube. Arch. Ophthalmol. 103:1582, 1985.
10. Nagashima, K.: Fistulous tract after conjunctivodacryocystorhinostomy. Ophthalmic Surg. 17:809, 1986.

Secondary Hemorrhage in Traumatic Hyphema

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We analyzed the records of 132 patients hospitalized between July 1986 and February 1989 for management of traumatic hyphema. The incidence of secondary hemorrhage was compared between patients treated with or without systemic administration of aminocaproic acid in addition to an otherwise identical protocol. Results among patients who were examined within one day of injury disclosed a 4.8% secondary hemorrhage rate in aminocaproic acid–treated patients (three of 63 patients) compared with a 5.4% rate in the patients not treated with aminocaproic acid (three of 56 patients, P = .31). All six patients sustaining secondary hemorrhage recovered visual acuities of 20/40 or better, with five of six patients achieving 20/20 visual acuities. A separate group of 13 patients who were examined more than one day after injury were found to have a secondary hemorrhage rate of 38.5% (five of 13 patients). Macular injury, not secondary hemorrhage, was most often responsible among those patients suffering permanent visual loss. In this study of a predominantly white population, patients had a relatively low incidence of secondary hemorrhage and did not demonstrate detectable benefit from aminocaproic acid administration. Because of the recognized side effects and cost of treatment, further analysis to determine which patients will benefit from treatment with aminocaproic acid is indicated.

MEDICAL MANAGEMENT of traumatic hyphema is debated. Treatment is primarily directed at identification and treatment of associated ocular and adnexal injuries, management of increased intraocular pressure, and the prevention of secondary hemorrhage. The incidence of secondary hemorrhage is reported to be between 3.5% and 38%,[1-10] varying with the population studied. Secondary hemorrhages are generally more severe than primary hemorrhages and predispose to vision-threatening conditions such as corneal blood staining, peripheral anterior synechiae, and secondary glaucoma. Because of these and other factors, patients who suffer a secondary hemorrhage may be more likely to require an operation and are reported to have a worse visual prognosis.[11,12]

Treatment to reduce the risk of secondary hemorrhage has included hospital admission with bed rest,[13,14] miotics,[15] eye patching,[16] and corticosteroid treatment.[1,17-20] Of these, only treatment with corticosteroids has been shown to alter the course of disease.[18] Although Spoor, Hammer, and Belloso[21] failed to show a corticosteroid effect on secondary hemorrhage, a recent study[18] reported a low secondary hemorrhage rate (7.1%) in patients treated with systemic corticosteroids. In this study, the secondary hemorrhage rate was the same as that in aminocaproic acid–treated patients and was markedly lower than that reported previously in controls from the same institution.[9,10] Three randomized, double-blind studies have shown that treatment with aminocaproic acid markedly reduces the risk of secondary hemorrhage in patients with traumatic hyphema.[4,9,10] Other studies have not shown that treatment with aminocaproic acid is beneficial.[8,22] Because of the variability in reported secondary hemorrhage rates and in the frequency and severity of complications associated with secondary hemorrhage, ophthalmologists have not universally accepted aminocaproic acid use as the standard treatment of patients with traumatic hyphema.[8,22-25]

We studied the records of patients seen at the emergency room at the Massachusetts Eye and Ear Infirmary to determine the incidence of secondary hemorrhage in our predominantly white New England population and to evaluate

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the impact of aminocaproic acid treatment on secondary hemorrhage rate.

Patients and Methods

All patients admitted with a traumatic hyphema between July 1986 and February 1989 were identified through their records in the emergency department of the Massachusetts Eye and Ear Infirmary. Hyphema was diagnosed if layered blood was observed in the anterior chamber or if dispersed red blood cells were observed. Patients with ruptured globes were excluded. One hundred forty-five patients were identified. Of these, three patients were ineligible because they left against medical advice before treatment, three had sustained postoperative hyphemas, and seven were discharged for outpatient care to their local ophthalmologists before five full days of hospital treatment. Of the remaining 132 patients, 13 were admitted to the emergency room more than 24 hours after sustaining injury and were considered a separate subgroup. The remaining 119 patients were admitted less than 24 hours after injury with a primary traumatic hyphema.

Information obtained from each patient included age, gender, race, nature of injury, duration of time between injury and initial examination, and complete medical history. Clinical data obtained at the time of initial examination included visual acuity, size of hyphema (as previously outlined by Read and Goldberg[11]), associated ocular and adnexal injury, and general physical examination. Treatment for all 119 patients followed a routine protocol including the following: admission to the hospital with activity restriction (limited ambulation permitted), elevation of the head of the bed to 30 degrees, protective shield, avoidance of aspirin-containing products, use of a topical cycloplegic, topical corticosteroids (equivalent to 1% prednisolone acetate, four times a day), and antiglaucoma medications as indicated. Sixty-three of the patients were treated with aminocaproic acid orally, 50 mg/kg of body weight every four hours for five days.

Patients admitted in the first year of the period studied were routinely treated with aminocaproic acid, which was the institutional practice at the time. During the second year, patients were randomly assigned to aminocaproic acid treatment or no treatment and during the last few months of the second year, the decision was primarily that of the admitting clinician. Sickle cell screening was performed on all nonwhite patients.

Patients were examined at least once daily by at least two physicians, at which time visual acuity, and results of slit-lamp and fundus examinations and applanation tensions were recorded. Secondary hemorrhage was diagnosed if the size of the hyphema increased or if fresh blood was present in the anterior chamber. Increased intraocular pressure (greater than 25 mm Hg) was treated with topical aqueous suppressants (timolol maleate, 0.5%). Oral acetazolamide sodium was added to the treatment regimen if needed. Follow-up information (final examination from six weeks to one year) on each patient included final visual acuity, tension, surgical procedures required, and permanent ocular sequelae of injury. All side effects from aminocaproic acid were noted. Statistical analysis comparing the rates of secondary hemorrhaging and population analysis were performed with the Fisher exact test, chi-square test, and Kolmogorov-Smirnov two-sample test.

Results

One hundred nineteen patients were admitted within 24 hours of injury with a primary traumatic hyphema, including 103 (87%) males and 16 (16%) females. One hundred eleven patients were white and eight were black. Aminocaproic acid was used in 63 patients whereas 56 patients received identical medical treatment without aminocaproic acid. Age and race data along with the results of the initial examination were analyzed (Table 1). Age, gender, initial visual acuity, height of initial hyphema, and associated ocular injuries were not significantly different between the two groups. Treatment was prematurely discontinued in six of the 63 patients initially treated with aminocaproic acid (10%) because of side effects including systemic hypotension, fever, rash, nausea, and vomiting.

Secondary hemorrhage occurred in six of the 119 patients (5%), three from each of the two treatment groups, and this rate was not significantly different between the two groups ($P = .31$). Of these six patients, none was black and four were men. At initial examination five of the six had hyphemas filling less than one third of the anterior chamber; the other had an initial

TABLE 1
RESULTS OF INITIAL EXAMINATION OF PATIENTS WITH TRAUMATIC HYPHEMA

	PATIENTS TREATED WITH AMINOCAPROIC ACID (N = 63)	PATIENTS NOT TREATED WITH AMINOCAPROIC ACID (N = 56)	CHI-SQUARE P VALUE
Gender (M, F)	55, 8	47, 9	.5
Race (white, nonwhite)	58, 5	52, 4	.5
Age (yrs, mean ± SD)	26.1 ± 10.8	19.5 ± 10.5	.10*
Eye affected (right, left)	28, 35	30, 26	.5
Hyphema height			
< ⅓ of anterior chamber	48	48	.2
⅓-½ of anterior chamber	11	4	—
½ to entire anterior chamber	3	2	—
Total	1	2	—
Visual acuity			
>20/40	21	17	.5
20/50-20/100	9	9	—
20/200-20/400	3	5	—
< 20/400	30	25	—
Intraocular pressure (mm Hg, mean ± SD)	19.3 ± 8.0	18.5 ± 7.6	.5†

*Determined by Kolmogorov-Smirnov two-sample test.
†Determined by *t*-test.

hyphema height of less than one half of the chamber height. Four patients had increased intraocular pressure and two had normal intraocular pressure. After resolution of the secondary hemorrhage, all six patients had a final visual acuity of 20/40 or better; five were 20/20. In patients without secondary hemorrhage, nine (8%) suffered a decrease in visual acuity to ≤ 20/400 after a minimum of six weeks' follow-up. Macular injury was responsible for this visual acuity reduction in eight of these patients, whereas lens changes accounted for the visual acuity reduction in the final patient. Overall, 21 patients sustained some degree of lens opacification, with ten patients subsequently undergoing cataract extraction or cataract extraction combined with a vitreoretinal procedure. Twelve other patients required an operation (Table 2). Angle recession and iris injury were the most common permanent sequelae (Table 3).

Of the 63 patients treated with aminocaproic acid, nine (14%) had rapid clot dissolution with an increase in intraocular pressure (previously described as pseudosecondary hemorrhages) after aminocaproic acid treatment was discontinued five days after hyphema. Five of these cases have been reported previously.[26]

A separate group of 13 patients, admitted more than 24 hours after their injuries, was examined. This group consisted of 12 males and one female. Six of the 13 patients were black (46%) and seven were white (54%; Table 4). Secondary hemorrhages occurred during hospitalization in five of these 13 patients (38%). Three of these patients were black. Two of the five patients had secondary hemorrhages at least twice during the hospital stay. Four of the 13 patients (31%) who were admitted more

TABLE 2
SURGICAL PROCEDURES REQUIRED IN PATIENTS WITH TRAUMATIC HYPHEMA EXAMINED WITHIN 24 HOURS OF INJURY

TYPE OF OPERATION	NO. OF PATIENTS (% OF TOTAL)
Cataract extraction	10 (8)
Vitrectomy	5 (4)
Exploration to rule out globe rupture	3 (3)
Photocoagulation or cryotherapy of retinal tear	2 (2)
Scleral buckle	1 (1)
Strabismus operation	1 (1)

TABLE 3
PERMANENT SEQUELAE IN ALL PATIENTS WITH TRAUMATIC HYPHEMA

COMPLICATION	NO. OF PATIENTS (% OF TOTAL)
Angle recession	47 (36)
Iris injury	31 (23)
Cataract	21 (16)
Retinal scar	10 (8)
Choroidal rupture	5 (4)
Persistently increased intraocular pressure	5 (4)
Corneal blood staining	3 (2)
Strabismus	2 (2)
Epiretinal membrane	2 (2)
Retinal tear	2 (2)
Retinal detachment	1 (1)
Macular hole	1 (1)
Optic neuropathy	1 (1)
Corneal scar	1 (1)

than 24 hours after injury required anterior chamber washout and one required cataract extraction. One patient required two anterior chamber washouts. Of the five patients who had secondary hemorrhages, four had final visual acuities of 20/40 or better.

Discussion

In contrast to previous studies,[4,9,10] our patients had a low rate of hyphema secondary hemorrhaging. The reason for this difference is obscure but may reflect an inherent difference in the populations studied. Traumatic hyphema studies performed in areas with predominantly white populations (Great Britain, Canada, Northern Europe, Minnesota, and Australia) have all demonstrated secondary hemorrhage rates of less than 10%.[22,25,27-31] Three studies have demonstrated a markedly higher rate of secondary hemorrhage in blacks compared to that in whites.[6,32,33] Other studies have failed to demonstrate a notable difference in secondary hemorrhage rates between whites and blacks.[9,34,35]

The variability in secondary hemorrhage rates may be dependent on factors other than race. None of our eight black patients who had acute hyphema suffered secondary hemorrhages. Differences in age, duration between injury and initial examination, the size of initial hemorrhage, the use of aspirin, and whether patients are hospitalized must also be considered. Although none of our patients received aspirin

TABLE 4
RESULTS IN PATIENTS WITH DELAYED INITIAL EXAMINATION

	PATIENTS TREATED WITH AMINOCAPROIC ACID (N = 8)	PATIENTS NOT TREATED WITH AMINOCAPROIC ACID (N = 5)	CHI-SQUARE P VALUE
Gender (M, F)	7, 1	5, 0	.2
Race (white, nonwhite)	6, 2	1, 4	.05
Age (yrs, mean ± SD)	25.6 ± 12.4	16.2 ± 7.0	.05*
Eye affected (right, left)	5, 3	3, 2	.5
Hyphema height			
< ⅓ of anterior chamber	2	3	.2
⅓-½ of anterior chamber	3	1	—
½ to entire anterior chamber		1	—
Total	3	0	—
Visual acuity			
>20/40	0	1	.1
20/50-20/100	1	3	—
20/200-20/400	1	0	—
< 20/400	6	1	—
Intraocular pressure (mm Hg, mean ± SD)	20.6 ± 8.8	11.3 ± 2.1	.05†

*Determined by Kolmogorov-Smirnov two-sample test.
†Determined by *t*-test.

during hospitalization because of its recognized effect on secondary hemorrhage rates,[36,37] recent use before injury was not assessed. Although not routinely used in series with low secondary hemorrhage rates, perhaps the use of topical corticosteroids and cycloplegic agents in our patients contributed to the low secondary hemorrhage rate.

Other studies have correlated size of initial hyphema with likelihood of secondary hemorrhage.[6] We did not identify this or any other notable characteristics at initial examination as being predictive of secondary hemorrhage, except for the duration between injury and initial examination. The risk of secondary hemorrhage during hospitalization was significantly greater among patients who were examined more than 24 hours after their injuries (5% vs 38.5%, $P = .001$). Whether these patients were examined because they developed a secondary hemorrhage with worsening symptoms or they represent a subgroup of patients with less access to health care is not clear. In either case, these patients appeared particularly prone to secondary hemorrhage as they hemorrhaged during hospitalization whether treated with aminocaproic acid or not. Further evaluation of this group of patients appears warranted to identify contributing risk factors.

Treatment with aminocaproic acid did not seem to influence the incidence of secondary hemorrhage episodes (4.8% vs 5.4%). This rate is markedly lower than in other studies in which the incidence of secondary hemorrhage in placebo-treated patients was 33%, 33%, and 23%, respectively.[4,9,10] In these well-controlled studies with large secondary hemorrhage rates, treatment with aminocaproic acid was shown to be effective in markedly decreasing the incidence of secondary hemorrhages. The actual efficacy of aminocaproic acid in preventing secondary hemorrhages cannot, however, be assessed from our study given the study design, population size, and the low secondary hemorrhage rate in both groups.

The use of any agent should be decided on the basis of potential risks and benefits of the treatment and also on the incidence of the condition in the population of untreated patients. Consideration must be given to the adverse effects of aminocaproic acid treatment, including pruritus, nausea and vomiting, muscle cramps, nasal stuffiness, rash, arrhythmias, confusional states, hypotension, and pseudosecondary hemorrhages. These can develop in up to 50% of patients.[4,22] For instance, two of our treated patients suffered falls with resultant facial lacerations that required suturing.

With a relatively low rate of secondary hemorrhage in our population and the liabilities of aminocaproic acid treatment (primarily cost and side effects), the final consideration must be given to the importance of prevention of secondary hemorrhage. Generally, it is thought that secondary hemorrhage increases the likelihood of glaucoma and worsens the visual prognosis. Many proponents of the use of aminocaproic acid cite the work of Gilbert and Jensen[12] who in 1973 reviewed the literature and concluded, on the basis of seven previously reported studies and their own patients, that patients with secondary hemorrhage have a worse visual prognosis. They believed that glaucoma and corneal blood staining were the main causes of visual loss in secondary hemorrhage. Other more recent studies have failed to correlate worse visual outcome with secondary hemorrhage.[4,8,25,34,38] Moreover, although none of our patients examined in the acute period after injury who developed secondary hemorrhages required surgical intervention, with the modern microsurgical technique of anterior chamber washout, the problems of corneal blood staining and acute glaucoma associated with secondary hemorrhage can usually be managed successfully.

Visual outcome in our population was much more dependent on concurrent injuries sustained acutely (specifically, macular damage) than on recurrent bleeding in the anterior chamber. Ten of the 11 (91%) patients sustaining secondary hemorrhages in this series (both acute and delayed examination) had final visual acuities of 20/40 or better. In contrast, macular injury, including choroidal rupture, scar formation, epiretinal membrane formation, and macular hole caused visual acuity loss to 20/400 or worse in eight (6%) patients who did not have secondary hemorrhages.

Nearly 20% (21 of 132) of our patients with traumatic hyphema developed some lens changes and ten required cataract extraction. Although angle recession and iris injury were the most commonly identified permanent sequelae, persistent increase in intraocular pressure developed in only five patients. Corneal blood staining was seen in only three patients (all had delayed examination), and only one occurred in conjunction with secondary hemorrhage.

In our study, patients with traumatic hyphema who were examined immediately after injury showed no significant difference in the incidence of secondary hemorrhage with or without aminocaproic acid administration when treated in a standard fashion with hospitalization, topical corticosteroids, and cycloplegia. Ninety-five percent (113 of 119) of patients examined within 24 hours of injury did not sustain secondary hemorrhage and even when it occurred, secondary hemorrhage was not associated with worsening of the visual prognosis. These results suggest that aminocaproic acid was of questionable benefit in our predominantly white population and that its use may not be warranted if side effects and cost effectiveness are considered. However, patients examined more than 24 hours after injury had a statistically significant ($P = .001$) higher rate of secondary hemorrhage and represent a unique population that deserves special consideration. There may be distinct subsets of the population who would benefit from aminocaproic acid treatment (blacks and patients with delayed examination). Our study was not specifically designed to evaluate appropriately its efficacy in a prospective fashion. Nevertheless, we were unable to demonstrate a beneficial effect of aminocaproic acid, and do not advocate its routine use in uncomplicated acute hyphema in populations similar to ours. Additionally, macular injury resulting from the initial trauma more closely relates to final visual outcome than the occurrence of secondary hemorrhage.

References

1. Yasuna, E.: Management of traumatic hyphema. Arch. Ophthalmol. 91:190, 1974.
2. Thygeson, P., and Beard, C.: Observations on traumatic hyphema. Am. J. Ophthalmol. 35:977, 1952.
3. Edwards, W. C., and Layden, W. E.: Traumatic hyphema. A report of 184 consecutive cases. Am. J. Ophthalmol. 75:110, 1973.
4. Kutner, B., Fourman, S., Brein, K., Hobson, S., Mrvos, D., Sheppard, J., and Weisman, S.: Aminocaproic acid reduces the risk of secondary hemorrhage in patients with traumatic hyphema. Arch. Ophthalmol. 105:206, 1987.
5. Coles, W. H.: Traumatic hyphema. An analysis of 235 cases. South. Med. J. 61:813, 1968.
6. Spoor, T. C., Kwitko, G. M., O'Grady, J. M., and Ramocki, J. M.: Traumatic hyphema in an urban population. Am. J. Ophthalmol. 109:23, 1990.
7. Witteman, G. J., Brubaker, S. J., Johnson, M., and Marks, R. G.: The incidence of rebleeding in traumatic hyphema. Ann. Ophthalmol. 17:525, 1985.
8. Kennedy, R. H., and Brubaker, R. F.: Traumatic hyphema in a defined population. Am. J. Ophthalmol. 106:123, 1988.
9. Crouch, E. R., Jr., and Frenkel, M.: Aminocaproic acid in the treatment of traumatic hyphema. Am. J. Ophthalmol. 81:355, 1976.
10. McGetrick, J. J., Jampol, L. M., Goldberg, M. F., Frenkel, M., and Fiscella, R. G.: Aminocaproic acid decreases the risk of secondary hemorrhage after traumatic hyphema. Arch. Ophthalmol. 101:1031, 1983.
11. Read, J., and Goldberg, M. F.: Comparison of medical treatment for traumatic hyphema. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78:799, 1974.
12. Gilbert, H. D., and Jensen, A. D.: Atropine in the treatment of traumatic hyphema. Ann. Ophthalmol. 5:1297, 1973.
13. Spaeth, G. L., and Levy, P. M.: Traumatic hyphema. Its clinical characteristics and failure of estrogens to alter its course. A double-blind study. Am. J. Ophthalmol. 62:1098, 1966.
14. Wilson, F. M.: Traumatic hyphema. Pathogenesis and management. Ophthalmology 87:910, 1980.
15. Rakusin, W.: Traumatic hyphema. Am. J. Ophthalmol. 74:284, 1972.
16. Edwards, W. C., and Layden, W. E.: Monocular vs binocular patching in traumatic hyphema. Am. J. Ophthalmol. 76:359, 1973.
17. Rynne, M. Y., and Romano, P. E.: Systemic corticosteroids in the treatment of traumatic hyphema. J. Pediatr. Ophthalmol. Strabismus 17:141, 1980.
18. Farber, M. D., Fiscella, R., and Goldberg, F.: Aminocaproic acid versus prednisone for the treatment of traumatic hyphema. A randomized clinical trial. Ophthalmology 98:279, 1991.
19. Oksala, A.: Treatment of traumatic hyphema. Br. J. Ophthalmol. 51:315, 1967.
20. Romano, P. E.: Pro steroids for systemic antifibrinolytic treatment for traumatic hyphema. J. Pediatr. Ophthalmol. Strabismus 23:92, 1986.
21. Spoor, T. C., Hammer, M., and Belloso, H.: Traumatic hyphema. Failure of steroids to alter its course. A double blind prospective study. Arch. Ophthalmol. 98:116, 1980.
22. Kraft, S. P., Christianson, M. D., Crawford, J. S., Wagman, R. D., and Antoszyk, J. H.: Traumatic hyphema in children. Treatment with epsilon aminocaproic acid. Ophthalmology 94:1232, 1987.
23. Ophthalmology Journal Club: Aminocaproic acid (correspondence). Arch. Ophthalmol. 102:818, 1984.
24. Kraft, S. P., and Crawford, J. S.: Traumatic hyphema therapy (correspondence). Ophthalmology 95:709, 1988.
25. Kearns, P.: Traumatic hyphema. A retrospective study of 314 cases. Br. J. Ophthalmol. 75:137, 1991.
26. Dieste, M. C., Hersh, P. S., Kylstra, J. A., Lar-

rison, W. I., Frambach, D. A., and Shingleton, B. J.: Intraocular pressure increase associated with epsilon-aminocaproic acid therapy for traumatic hyphema. Am. J. Ophthalmol. 106:383, 1988.

27. Uusitalo, R. J., Saari, M. S., Aine, E., and Saari, K. M.: Tranexamic acid in the prevention of secondary hemorrhage after traumatic hyphema. Acta Ophthalmol. 59:539, 1981.

28. Bengtsson, E., and Ehinger, B.: Treatment of traumatic hyphema. Acta Ophthalmol. 53:914, 1975.

29. Agapitos, P. J., Noel, L. P., and Clarke, W. N.: Traumatic hyphema in children. Ophthalmology 94:1238, 1987.

30. Varnek, L., Daisgaard, C., Hansen, A., and Klie, F.: The effect of tranexamic acid on secondary hemorrhage after traumatic hyphema. Acta Ophthalmol. 58:787, 1980.

31. Sjolie, A. K., and Mortensen, K. K.: Traumatic hyphema treated ambulatory and without antifibrinolytic drugs. Acta Ophthalmol. 58:125, 1980.

32. Skalka, H. W.: Recurrent hemorrhage in traumatic hyphema. Ann. Ophthalmol. 10:1153, 1978.

33. Palmer, D. J., Goldberg, M. F., Frenkel, M., Fiscella, R., and Anderson, R. J.: A comparison of two dose regimens of epsilon aminocaproic acid in the prevention and management of secondary traumatic hyphemas. Ophthalmology 93:102, 1986.

34. Thomas, M. A., Parrish, R. K., and Feurer, W. J.: Rebleeding after traumatic hyphema. Arch. Ophthalmol. 104:206, 1986.

35. Kushner, A. G.: Traumatic hyphema. Surv. Ophthalmol. 4:2, 1959.

36. Gorn, R. A.: The detrimental effect of aspirin on hyphema rebleed. Ann. Ophthalmol. 11:351, 1979.

37. Ganley, J. P., Geiger, J. M., Clement, J. R., Rigby, P. G., and Levy, G. J.: Aspirin and recurrent hyphema after blunt ocular trauma (correspondence). Am. J. Ophthalmol. 96:797, 1983.

38. Uusitalo, R. J., Ranta-Kemppainen, L., and Tarkkanen, A.: Management of traumatic hyphema in children. An analysis of 340 cases. Arch. Ophthalmol. 106:1207, 1988.

OPHTHALMIC MINIATURE

It had occurred to Pecola some time ago that if her eyes, those eyes that held the pictures, and knew the sights—if those eyes of hers were different, that is to say, beautiful, she herself would be different. Her teeth were good, and at least her nose was not big and flat like some of those who were thought so cute. If she looked different, beautiful, maybe Cholly would be different, and Mrs. Breedlove too. Maybe they'd say, "Why, look at pretty-eyed Pecola. We mustn't do bad things in front of those pretty eyes."

Toni Morrison, *The Bluest Eye*
New York, Pocket Books, 1970, p. 40

Improvement in Visual Acuity in Chronic Aphakic and Pseudophakic Cystoid Macular Edema After Treatment With Topical 0.5% Ketorolac Tromethamine

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Ketorolac tromethamine 0.5% ophthalmic solution treatment was compared to placebo treatment in 120 patients with chronic aphakic or pseudophakic cystoid macular edema (six-month or more duration of distance visual acuity of 20/40 or less and angiographic evidence of cystoid changes) during a four- to five-month double-masked, multicenter study in which patients were randomly assigned. A statistically significant improvement in distance visual acuity (two lines or more) was observed in the ketorolac-treated group as compared to the placebo-treated group after 30 days (P = .038), 60 days (P = .017), and 90 days (P = .008) of treatment. This improvement in visual acuity remained statistically significant one month after cessation of treatment (P = .001). Nine ketorolac-treated patients and two placebo-treated patients demonstrated a decrease in visual acuity one month after treatment was discontinued. Seven of the nine ketorolac-treated patients experienced an improvement in visual acuity after retreatment as compared to none of the placebo-treated patients. This study offers evidence for a more optimistic outlook in the medical treatment of chronic aphakic and pseudophakic cystoid macular edema.

KETOROLAC TROMETHAMINE 0.5% ophthalmic solution is a new noncorticosteroidal, anti-inflammatory drug that is a cyclo-oxygenase inhibitor. In a previous study,[1] 60 days of treatment with ketorolac was compared with treatment with placebo in a double-masked, randomized, single-center study involving 30 patients with chronic aphakic and pseudophakic cystoid macular edema of at least four months' duration. All patients had angiographically confirmed aphakic or pseudophakic cystoid macular edema and distance visual acuities of 20/40 or less. At the end of treatment, improvement in visual acuity of two lines or more was seen in more ketorolac-treated patients than in placebo-treated patients (P = .005). The purpose of our double-masked, randomized, placebo-controlled study was to evaluate further the visual acuity effects of treatment with this new cyclo-oxygenase inhibitor when applied for 90 days on a larger group of patients with chronic aphakic or pseudophakic cystoid macular edema (six-month or more duration of distance visual acuity of 20/40 or less and fluorescein angiographic evidence) enrolled from several medical centers.

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Material and Methods

One hundred twenty aphakic and pseudophakic patients with reduced visual acuity (distance visual acuity of 20/40 or less) for six months or more associated with clinical and fluorescein angiographic evidence of cystoid macular edema were randomly assigned, in a double-masked fashion, to treatment with either ketorolac tromethamine 0.5% ophthalmic solution or placebo-vehicle solution. These patients were enrolled by 12 investigators from ten medical centers. Informed consent was obtained from each patient who participated in this four- to five-month clinical study.

Patient exclusion criteria included the following: (1) a distance visual acuity that was better than 20/40; (2) a baseline fluorescein angiogram that was not consistent with cystoid macular edema; (3) use of local or systemic anti-inflammatory drugs (corticosteroids, nonsteroidal anti-inflammatory drugs, or more than two 325-mg tablets of aspirin daily) within the preceding six weeks; (4) ocular disease preventing adequate examination of the anterior segment of the eye or retina; (5) unstable diabetes or systemic hypertension; (6) preexisting macular disease preventing adequate retinal examination for the presence of cystoid macular edema; and (7) a history of cystoid macular edema for less than six months' duration. Patients were enrolled in the study with or without an intraocular lens and with or without a history of multiple ocular operations. No attempt was made by the investigators to determine whether the intraocular lens in pseudophakic patients had ultraviolet-absorbing properties.

An ocular examination was performed on each patient within the two weeks before study enrollment to confirm the diagnosis of chronic aphakic or pseudophakic cystoid macular edema and to rule out the presence of exclusion criteria. Visual acuity was determined at distance using Snellen testing after a careful refraction. Biomicroscopic slit-lamp examinations of the periocular areas and external eye were performed. A dilated retinal examination was performed using direct and indirect ophthalmoscopy to diagnose chronic cystoid macular edema tentatively, after which fluorescein angiography was performed to confirm the diagnosis. Although a contact-lens examination was not performed to avoid interfering with fluorescein angiography, a Hruby lens examination of the macula was encouraged in all patients. Intraocular pressures were measured by Goldmann applanation tonometry or its equivalent. All patients in the study received identical, complete ocular examinations at baseline, and at 30, 60, 90, and 120 days after the initiation of treatment and, depending on their response to cessation of treatment, 150 days after enrollment. Fluorescein angiography was performed and graded at baseline and 90 days after initiation of treatment.[2]

Snellen distance visual acuity was chosen as the primary efficacy variable. Therefore, special attention was given to this measurement. All visual acuities were determined by one person after a careful refraction performed in the same examination room with identical lighting at baseline and at 30, 60, 90, 120, and 150 days after initiation of treatment. During each distance visual acuity determination, the row of letters most characteristic of the patient's visual acuity was selected by the individual performing the refraction. Minuses and pluses (the usual means of recording Snellen measurements) were not permitted as the final recorded visual acuity notation for visits. Visual acuity determination was the primary task of one person. This person was unaware of treatments, angiograms, and details of the clinical examination.

Within two weeks after the baseline examination, each patient began a 90-day treatment regimen (0.05 ml, or one drop, four times daily in the involved eye) with either ketorolac tromethamine 0.5% ophthalmic solution or placebo solution of the same pH and tonicity packaged in identical containers. Treatment was assigned by a computer-generated predetermined randomization schedule. Each patient returned for complete ocular examination at 30, 60, and 90 days after initiation of treatment. At each visit the investigator took the preceding month's bottle, examined it for evidence of proper use, and replaced it with the next month's treatment bottle. Treatment was discontinued at 90 days. At 120 days (after one month without treatment) each patient received their fifth complete ocular examination. If distance visual acuity had decreased by two or more lines as compared to the measurement at 90 days, treatment was reinstituted with the remaining bottle of the same treatment solution in a double-masked fashion. The last possible patient examination was on Day 150. No patient was treated with either solution for more than a total of 120 days during this study.

Results

One hundred twenty patients were enrolled by 12 investigators in this multicenter clinical study during approximately 3½ years: R. Campo (ten patients), H. Cupples (nine patients), A. Flach (ten patients), L. Jampol and D. Weinberg (nine patients), M. Kraff (27 patients), W. Lefler (nine patients), A. Neumann (ten patients), J. Pulido (nine patients), S. Severin (two patients), G. Tate (two patients), and L. Yannuzzi (33 patients). These patients were treated with either ketorolac tromethamine 0.5% ophthalmic solution (61 patients) or placebo-vehicle solution (59 patients). The two treatment groups were comparable in terms of age, gender, ethnic origin, concurrent systemic disease, initial visual acuity, baseline fluorescein angiogram grade, pupil shape, intraocular lenses, the presence of vitreous humor in the anterior chamber or to the surgical wound, and the presence of synechia. From this initial enrollment, 113 patients were examined at 30 days of treatment, 106 were examined at 60 days of treatment, 95 were examined at 90 days of treatment, and 87 were examined at 120 days of treatment after not having been treated for 30 days. Patients did not have an examination as scheduled for the following reasons: (1) missed a visit, (2) systemic illness, (3) poor compliance, or (4) moved to a new residence. Treatment groups were not statistically different in terms of these missing examinations. At the 120-day examination, nine ketorolac-treated and two placebo-treated patients had a decrease in distance visual acuity and they were retreated at five months in a double-masked fashion.

Patients treated with ketorolac 0.5% demonstrated a statistically significant improvement ($P < .05$) in distance visual acuity as compared to placebo-treated patients at each monthly examination (Table). This improvement in distance visual acuity was statistically significant ($P < .05$) at each monthly examination including the 120-day examination that was performed after one month of no treatment. After cessation of treatment, nine cyclo-oxygenase inhibitor–treated patients and two placebo-treated patients demonstrated a decrease in visual acuity. Seven cyclo-oxygenase inhibitor–treated patients had a return in visual acuity after retreatment, but no placebo-treated patient responded to retreatment. Five patients treated with ketorolac and 13 patients treated with placebo demonstrated a decrease in distance visual acuity during treatment.

The ocular adverse events in our study showed no marked difference between treatment groups. The number and severity of these adverse events were not statistically different between groups. Additionally, slit-lamp examinations were performed at baseline, 30, 60, 90, and 120 days after the initiation of treatment. These examinations included the diagnosis, if present; and the grading (none, mild, moderate, or severe) of eyelid edema, chemosis, ciliary flush, anterior chamber cells and flare, keratitis, superior and central corneal edema, and presence of folds in Descemet's membrane. The severity of these ocular signs was not statistically different between the ketorolac and placebo treatment groups. Initial intraocular pressures were slightly lower in the ketorolac-treated group. Results at follow-up visits were analyzed with analysis of covariance, using pretreatment intraocular pressure as covariant,

TABLE
IMPROVEMENT IN SNELLEN DISTANCE VISUAL ACUITY (2 LINES OR MORE)

	TREATMENT (IMPROVEMENT/TREATED)		
EXAMINATION TIME	KETOROLAC (61 ENROLLED)	PLACEBO (59 ENROLLED)	P VALUE*
30 days (one month of treatment)	19/56	10/57	.038
60 days (two months of treatment)	20/54	9/52	.017
90 days (three months of treatment)	22/46	10/49	.008
120 days (one month without treatment)	21/41	7/46	.001
150 days (one month without treatment and one month of retreatment)	7/9	0/2	—

*Cochran-Mantel-Haenszel test.

and no treatment effect on intraocular pressure was statistically evident. Therefore, it appears both treatments were tolerated well.

Discussion

The results of our double-masked, placebo-controlled, randomized, multicenter study confirmed the results of a smaller study that reported that treatment with ketorolac tromethamine 0.5% ophthalmic solution for 60 days may provide an improvement in visual acuity in patients with chronic aphakic and pseudophakic cystoid macular edema.[1] We observed a statistically significant improvement ($P < .05$) in distance visual acuity at each month of examination in the group of patients treated with the cyclo-oxygenase inhibitor as compared to the group treated with placebo (Table). Unlike the previous study, the improvement in visual acuity remained statistically significant ($P < .05$) 30 days after the cessation of treatment. This difference may be related to the different population size (30 vs 120 patients enrolled) or to the different duration of treatment (60 days vs 90 days) in each study. The magnitude of the change in visual acuity observed averaged 3.6 Snellen lines of improvement, with a range of two to nine lines. Three supplemental analyses of Snellen visual acuity improvement were conducted to determine the potential influence of the following pretreatment variables: (1) initial visual acuity, (2) type of intraocular lens, (3) coexistent vascular disease, and (4) baseline angiogram grade. These analyses used Cochran-Mantel Haenszel methodology, stratified by each variable. Two lines or more of Snellen visual improvement in distance visual acuities were analyzed with the Pearson chi-square test and a two-tailed Fisher's exact *t*-test. After adjusting for these variables, ketorolac's beneficial effect on visual acuity remained statistically significant compared to that of placebo ($P < .05$).

Other studies may not have demonstrated a statistically significant improvement in visual acuity during treatment of chronic aphakic and pseudophakic cystoid macular edema with cyclo-oxygenase pathway–inhibiting drugs for the following reasons: (1) ketorolac may be more effective than other cyclo-oxygenase inhibitors for the treatment of chronic aphakic and pseudophakic cystoid macular edema; (2) the treatment groups in the ketorolac studies may not be comparable, thereby preventing a reliable comparison between the drug and placebo treatments; (3) the patient population from which participants were chosen for the ketorolac studies may be unique and unrepresentative of patient populations in which other drugs were tested; and (4) the design of the recently reported ketorolac studies may be unlike that of the other studies reported in the literature and this unique design could explain the positive results.

Ketorolac tromethamine is the first parenteral nonsteroidal anti-inflammatory drug to become available for analgesic use in the United States. It appears to be as effective as morphine or meperidine for short-term relief of moderate to severe pain, without respiratory depression.[3] Additionally, it has impressive anti-inflammatory properties.[4] This new cyclo-oxygenase inhibitor appears to be more effective and less toxic than many other cyclo-oxygenase inhibitors when tested after topical application in laboratory experiments.[5] After a cataract operation, this anti-inflammatory ophthalmic solution decreased postoperative inflammation to a greater extent than did placebo treatment.[6] Furthermore, it has demonstrated the ability to prevent angiographic cystoid macular edema in association with a cataract operation when administered pre- and postoperatively without concurrent use of corticosteroids.[7] This effect has not been studied in other cyclo-oxygenase inhibitors. Therefore, it is possible that ketorolac may be more effective than other cyclo-oxygenase inhibitors for the treatment of chronic aphakic or pseudophakic cystoid macular edema. Although it has been approved for use as an ophthalmic solution in other parts of the world, it is not yet commercially available in the United States.

As described in the results, the ketorolac and placebo treatment groups in this study were comparable in all pretreatment characteristics except intraocular pressure. However, the groups may have differed in terms of other important variables that were not recognized during our study. For example, the light-transmission characteristics of the intraocular lenses were not compared in the two treatment groups, and the effects of light may be an important factor in initiating or perpetuating chronic aphakic and pseudophakic cystoid macular edema.[8] Beyond the enrollment requirement of the minimal six-month duration of cystoid macular edema, the duration of these changes was not determined in each patient.

The duration of the decreased visual acuity and the coexistent macular cystoid changes may influence a patient's response to treatment. In addition to these potentially important variables, many other, as yet unrecognized, factors that may influence the pathogenesis of chronic aphakic and pseudophakic cystoid macular edema undoubtedly exist. Any one of these known or unknown variables could influence the results of this clinical study. The randomized, double-masked, multicenter design of this study should have distributed these potentially important, but unrecognized or ignored biases, equally between the treatment and control groups. However, the inability to confirm, in retrospect, that these variables are distributed equally weakens the study.

The design and execution of our study was influenced by the experience gained during the pilot study.[1] This experience provided a means of avoiding many of the potential problems that have hindered the evaluation of response to the medical treatment of chronic aphakic and pseudophakic cystoid macular edema in the past. These potential problems include the following: (1) informed consent; (2) patient compliance; (3) difficulties performing and interpreting fluorescein angiography; (4) concurrence of cystoid macular edema in some systemic diseases; (5) difficulty and confusion in evaluating the severity of chronic aphakic and pseudophakic cystoid macular edema; (6) appropriate patient inclusion and exclusion criteria; (7) duration of treatment; (8) the tendency for chronic aphakic and pseudophakic macular edema to undergo spontaneous resolution; and (9) proper selection of study population size. The importance of recognizing these potential problems during the design of a clinical study of the efficacy of a medical treatment for chronic aphakic and pseudophakic cystoid macular edema has been discussed previously as was the rationale underlying our study design.[1] Our study differs from this pilot study in that it is a larger, multicenter study and it includes a longer treatment duration. However, the basic design of the study and the primary efficacy variable (distance visual acuity) remain the same.

Although fluorescein angiograms confirming cystoid macular edema were necessary for patient inclusion in our study, they were not considered an efficacy factor. Investigators have shown that angiogram grade corresponds poorly with Snellen visual acuity.[2] Although in a large multicenter study of vitrectomy for chronic aphakic cystoid macular edema the angiographic course was parallel to the visual course, the association was not close enough to show a notable correlation.[9] Although 16 of 46 ketorolac-treated patients and nine of 49 placebo-treated patients had improved angiograms in our study, it was not a statistically significant difference ($P = .10$). However, 11 of 46 ketorolac-treated patients as compared to two of 49 placebo-treated patients had improved angiograms and improvements in Snellen visual acuity, which is a statistically significant difference ($P = .01$). Therefore, the changes in angiograms within this study provide support for a treatment effect from the cyclo-oxygenase inhibition.

This study provides evidence that treatment with ketorolac improves visual acuity in chronic symptomatic aphakic and pseudophakic cystoid macular edema. However, the clinical benefit derived from cyclo-oxygenase inhibition treatment must be evaluated in the light of different potential medical and surgical treatments for this postoperative problem. For example, the incidence of cystoid macular edema can vary with the type of cataract operation[10-12] and the presence of ultraviolet light filters in intraocular lenses.[8,13] Additionally, a postoperative vitreous operation with conventional anterior vitrectomy or laser techniques may be useful in some patients with chronic aphakic or pseudophakic cystoid macular edema.[14-16] Furthermore, autacoids other than the prostaglandins (bradykinin, serotonin, histamine, neuropeptides, for example) may have a role in the pathogenesis of aphakic and pseudophakic cystoid macular edema.[17,18] Most importantly, the effect of corticosteroids on this postoperative complication should be evaluated. Finally, uncontrolled studies in small numbers of patients have suggested carbonic anhydrase inhibitors[19] or hyperbaric oxygen[20] may have potential benefit in the treatment of aphakic and pseudophakic cystoid macular edema. Therefore, the ultimate clinical effects of cyclo-oxygenase inhibitor administration for the prevention or treatment of aphakic or pseudophakic cystoid macular edema must be evaluated in relation to other possible pathogenic factors and their respective medical and surgical treatments.

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References

1. Flach, A. J., Dolan, B. J., and Irvine, A. R.: Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. Am. J. Ophthalmol. 103:479, 1987.
2. Yannuzzi, L. A.: Perspective on the treatment of aphakic cystoid macular edema. Surv. Ophthalmol. 28:540, 1984.
3. Ketorolac tromethamine. Med. Lett. Drugs Ther. 32:79, 1990.
4. Rooks, W. H., Maloney, P. J., Shott, L. D., Schuler, M. E., Sevelius, H., Strosberg, A. M., Tanenbaum, L., Tomolonis, A. J., Wallach, M. B., Waterbury, D., and Yee, J. P.: The analgesic and anti-inflammatory profile of ketorolac and its tromethamine salt. Drugs Exp. Clin. Res. 11:479, 1985.
5. Rooks, W. H., Maloney, P. J., Shott, L. D., and Waterbury, D.: The anti-inflammatory profile of ketorolac. Drugs Exp. Clin. Res. 11:479, 1985.
6. Flach, A. J., Lavelle, C. J., Olander, K. W., Retzloff, J. A., and Sorenson, L. W.: The effect of ketorolac tromethamine solution 0.5% in reducing postoperative inflammation after cataract extraction and intraocular lens implantation. Ophthalmology 95:1279, 1988.
7. Flach, A. J., Stegman, R. C., Graham, J., and Kruger, L. P.: Prophylaxis of aphakic cystoid macular edema without corticosteroids. A paired comparison, placebo-controlled, double-masked study. Ophthalmology 97:1253, 1990.
8. Jampol, L. M.: Aphakic cystoid macular edema. A hypothesis. Arch. Ophthalmol. 103:1134, 1985.
9. Fung, W. E.: Anterior vitrectomy for chronic aphakic cystoid macular edema. Ophthalmology 87:189, 1980.
10. Smith, R. T., Campbell, C. J., and Koester, C. J.: The barrier function in extracapsular cataract surgery. Ophthalmology 97:90, 1990.
11. Sorr, E. M., Everett, W. H., and Hurite, F. G.: Incidence of fluorescein angiographic subclinical macular edema following phacoemulsification of senile cataracts. Ophthalmology 86:2013, 1979.
12. Wetzig, P. C., Thatcher, D. B., and Christiansen, J. M.: The intracapsular versus extracapsular cataract technique in relationship to retinal problems. Trans. Am. Ophthalmol. Soc. 77:339, 1979.
13. Kraff, M. C., Sanders, D. R., and Jampol, L. M.: Effect of an ultraviolet filtering intraocular lens on cystoid macular edema. Ophthalmology 92:366, 1985.
14. Federman, J. L., Annesley, W. H., Jr., and Sarin, L. K.: Vitrectomy and cystoid macular edema. Ophthalmology 87:622, 1980.
15. Fung, W. E.: Surgical therapy for chronic aphakic cystoid macular edema. Ophthalmology 89:898, 1982.
16. Katzen, L. E., Fleischman, J. A., and Trokel, S.: YAG laser treatment of cystoid macular edema. Am. J. Ophthalmol. 95:589, 1983.
17. Bito, L. Z., Nichols, R., and Siminoff, S.: Ocular effects of substance P and other biologically active peptides as compared to prostaglandin E_2 (PGE_2). Proc. Int. Soc. Eye Res. 1:53, 1980.
18. Vane, J. R.: Prostaglandins as mediators of inflammation. Prostaglandin Thromboxane Res. 2:791, 1976.
19. Cox, S. N., Hay, E., and Bird, A. C.: Treatment of chronic macular edema with acetazolamide. Arch. Ophthalmol. 106:1190, 1988.
20. Pfoff, D. S., and Thom, S. R.: Cystoid macular edema treated with hyperbaric oxygen. Ophthalmology 97(suppl.):120, 1990.

Pathologic Findings of Photic Retinopathy in the Human Eye

W. Richard Green, M.D., and Dennis M. Robertson, M.D.

The macular retina of a patient whose eye was scheduled for enucleation because of progressive growth of a malignant melanoma that had invaded the iris and filtration angle was exposed to unfiltered light from the operating-room microscope for 60 minutes. Photic maculopathy was documented with fundus photography and fluorescein angiography 67 hours after light exposure. Seventy-two hours after light exposure, the eye was enucleated, fixed in Trumpe's solution, and studied with light microscopy and electron microscopy. Findings included localized necrosis of the retinal pigment epithelium; loss of the apical villi, plasma membranes, and cytoplasmic organelles; extrusion of pigment granules; and extensive disruption of the outer lamellae of the photoreceptors. The inner segments of the photoreceptors were edematous and contained swollen mitochondria. Near the margins of the photic retinopathy, thinned retinal pigment epithelial cells appeared to have migrated under injured retinal pigment epithelial cells, suggesting early attempts at repair. Additional findings included Müller-cell swelling.

PHOTIC RETINOPATHY caused by exposure to light from the operating-room microscope is a well-known entity and has been previously reported.[1-4] In recent experimental studies, Robertson and Feldman[5] and later Robertson and McLaren[6] deliberately induced photic retinopathy in human eyes, demonstrating that photic retinopathy could be induced by visible light when infrared and ultraviolet rays were filtered and that photic retinopathy was associated with a visual scotoma. We reported the light- and electron-microscopic findings of acute photic retinopathy induced in the macula of a human eye exposed to light from the operating-room microscope for 60 minutes 72 hours before enucleation for an iris melanoma.

Subject and Methods

A 49-year-old woman with a malignant melanoma of the left iris was observed over a nine-year interval during which the tumor progressively expanded and invaded the anterior chamber angle. With spectacle correction of R.E.: −1.50 − 0.50 × 75 and L.E.: −1.50 − 1.25 × 114, visual acuity was 20/20; other than the melanoma involving the anterior segment, the eye appeared to be normal by clinical examination. Enucleation was advised. Her motivation and attitude were appraised by one of us (D.M.R.). A protocol approved by the Mayo Clinic Institutional Review Board was reviewed and informed consent was obtained to expose the eye to light from the operating-room microscope before enucleation.

The pupil was maximally dilated, and the operating-room microscope was placed at the patient's side and focused at the pupillary plane. The trapezoidal hot-spot image of the microscope light source was oriented vertically. An eyelid speculum held the eyelids open. The eye was anesthetized with 0.5% proparacaine hydrochloride drops, and the cornea was intermittently bathed with balanced saline solution while the patient fixated on the center of the unfiltered light filament of a Zeiss OpMi-6 operating-room microscope (Carl Zeiss, Inc.,

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D-7082 Oberkochen, Germany) for 60 minutes. Radiometric measurements were calculated as in previous reports[5,6] and resulted in a source radiance of 2.5 watts/cm^2-sr, and a retinal irradiance of 0.450 watts/cm^2. Studies before and after exposure included clinical examination, color fundus photography, and fluorescein angiography.

Seventy-two hours after light exposure, the eye containing the melanoma was removed and immediately fixed in Trumpe's solution. The macular area was removed and hemisected horizontally at the area of the foveola. Half was processed for light microscopy and half was processed for transmission electron microscopy.

Results

Twenty-four hours after light exposure, the central visual acuity decreased from a preoperative value of 20/20 to 20/40 and the patient observed a vertically oriented oval-shaped blue-gray central scotoma that corresponded in size and shape with a gray macular lesion (approximately 1.5 × 1.0 mm) located at the area of the retinal pigment epithelium. In the center of the lesion, deep to the fovea, a focal yellow area approximately 250 μm in diameter that had a mother-of-pearl appearance was observed.

Forty-eight hours after light exposure, the photic lesion was no longer as well-delineated from the surrounding normal retina. The visual acuity was 20/50. The patient noticed no change in the appearance of the scotoma.

Sixty-seven hours after light exposure, the best-corrected visual acuity was 20/50, and the main area of photic retinopathy appeared as a disk-like lesion and was uniformly light brown in color. The central zone deep to the fovea remained yellow-white like mother-of-pearl but it was more confined than it had been at initial appearance at 24 hours (Fig. 1).

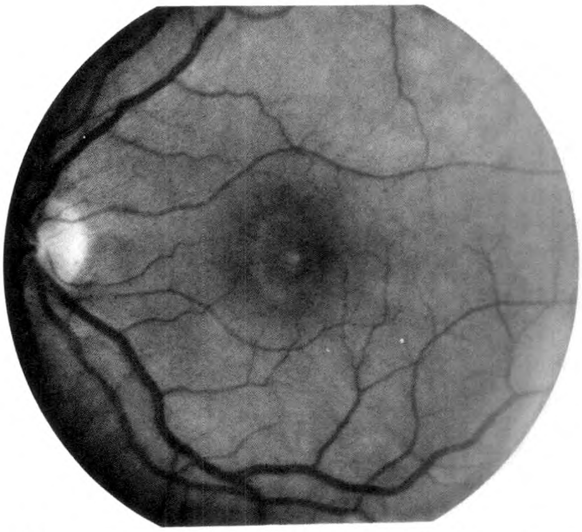

Fig. 1 (Green and Robertson). Ophthalmoscopic appearance of 49-year-old macula 67 hours after light exposure showing a vertically oriented light-brown discoloration centered in the macula at the level of the retinal pigment epithelium. The central light area at the fovea was yellow-white in clinical appearance.

A fluorescein angiogram 67 hours after light exposure showed progressive accumulation of dye at the area of the deep retina and the altered retinal pigment epithelium (Fig. 2). During the early arteriovenous phase, a central disk-like area of hyperfluorescence surrounded by a thin doughnut-like ring of hypofluorescence was observed, peripheral to which there was a halo of relative hyperfluorescence (Fig. 2, left). During the later phase of angiography, hyperfluorescence increased as dye progressively diffused into the deep retina (Fig. 2, right).

Light microscopy—Examination of the anterior segment disclosed a malignant melanoma composed primarily of spindle A-cells but with clusters of spindle B-cells, intermediate cells, and a few epithelioid cells. The tumor invaded the trabecular meshwork canal and the outflow channels, including Schlemm's canal.

Examination of 46 serial sections through half of the macula disclosed a central 1-mm area where an amorphous eosinophilic material largely replaced the disrupted outer segments, and a swollen stubby appearance of the inner segments and an edematous irregularly thickened retinal pigment epithelium were observed. At the site of the photic lesion, the nuclei of the retinal pigment epithelial cells were liquefied, whereas the adjacent retinal pigment epithelial cells showed a normal chromatin pattern. A few pigmented cells internal to the area of the retinal pigment epithelium were observed at the margins of the photic lesion. Elsewhere, the retina, retinal pigment epithelium, and choroid were unremarkable. The photoreceptor nuclei appeared relatively intact (Fig. 3).

Examination of 1-μm-thick Epon-embedded sections through the fovea disclosed the retina

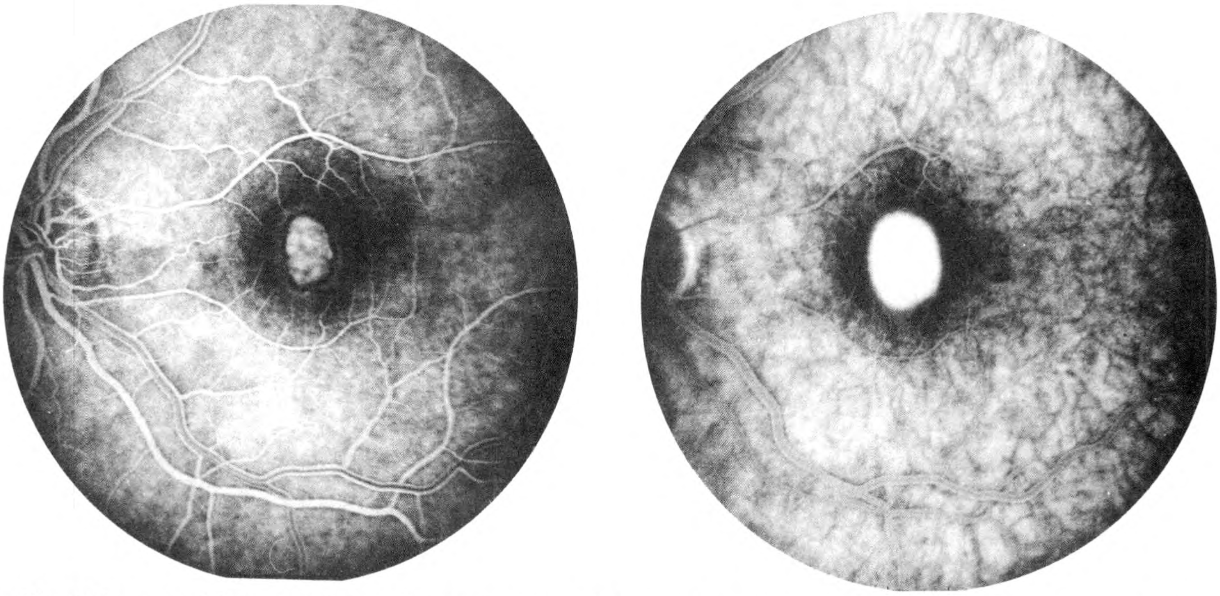

Fig. 2 (Green and Robertson). Arteriovenous phase of fluorescein angiogram (left) demonstrates hyperfluorescence in area of photic damage at the level of the retinal pigment epithelium (left). Notice the ring of hypofluorescence surrounded by a halo of hyperfluorescence at perimeter of the lesion. The microscopic findings that correlate with the varying intensity of the fluorescence are shown in Figures 4 and 5. Late phase of angiography (right) demonstrates dye diffusion into the deep retinal tissues.

to be detached by a thin layer of amorphous proteinaceous material extending over a distance of more than 1 mm. Here the outer segments were disrupted and the retinal pigment epithelium was swollen and partially degenerated. Adjacent to the photic retinopathy, the normal retinal pigment epithelial cells were thinned and partly depigmented where they appeared flattened with an increased diameter. At the perimeter of the photic retinopathy, retinal pigment epithelial cells appeared to have migrated under necrotic retinal pigment epithelial cells, which were displaced inward (Figs. 4 and 5).

Electron microscopy—Electron-microscopic examination disclosed marked swelling of the photoreceptor outer segments with separation of the cell membrane from distorted, compacted, and partially disintegrated lamellar disks (Fig. 6). A variably dense granular materi-

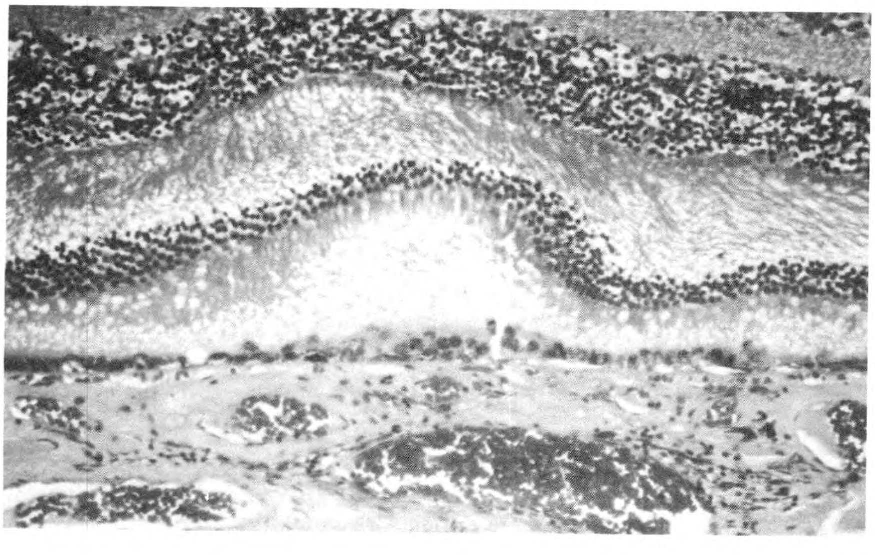

Fig. 3 (Green and Robertson). Light-microscopic appearance of photic retinopathy with edematous outer retina and the edematous irregularly thickened retinal pigment epithelium. Most of the retinal swelling involves the photoreceptor layer where an amorphous eosinophilic material largely replaces the outer segments. The photoreceptor nuclei appear relatively intact (hematoxylin and eosin stain, × 520).

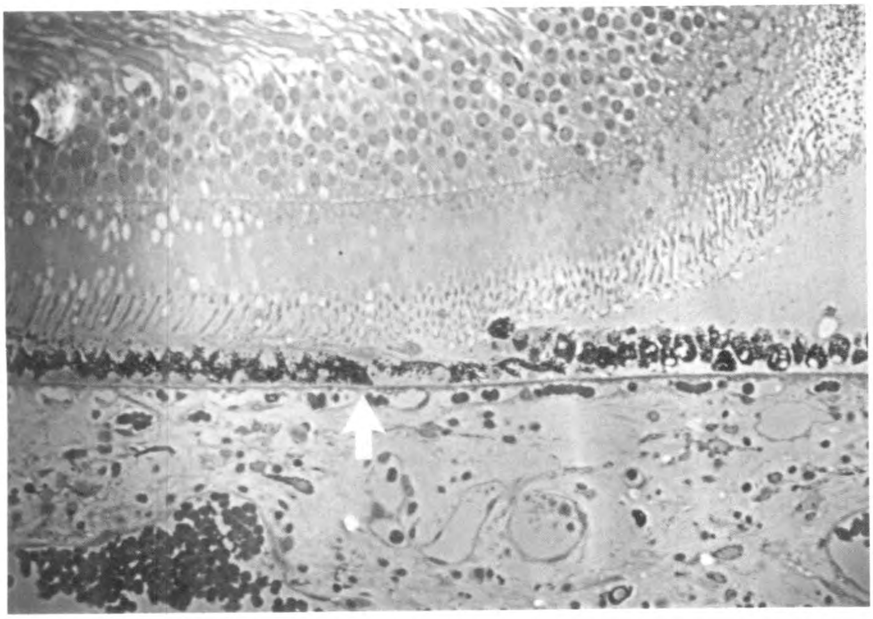

Fig. 4 (Green and Robertson). Light-microscopic appearance of an area of junction between lesion (right of arrow) and normal unaffected retina and retinal pigment epithelium (left of arrow). In the lesion, the retina is edematous. An amorphous material is observed in the area of disrupted outer segments of the photoreceptors and the subretinal space. The retinal pigment epithelial cells immediately to the right of the arrow are partly depigmented and slightly flattened. Further to the right, similar cells have apparently migrated under necrotic retinal pigment epithelial cells. The varying concentrations of pigment correlate with the varying intensity of the fluorescence at the perimeter of the retinopathy demonstrated in Figure 2 (paraphenylenediamine stain, × 520).

al was located between the outer segments and between the outer segments and the retinal pigment epithelium. The inner segments were swollen and had marked distention of the mitochondria. Many of the photoreceptor cells and some of the Müller cells in the outer nuclear area were slightly swollen with dissolution of cytoplasmic structures. The photoreceptor nuclei appeared normal.

The retinal pigment epithelium was moderately distended, had extensive loss of plasma membranes, apical villous processes, cytoplasmic organelles, and mild extrusion of pigment granules. Small areas of granular material were

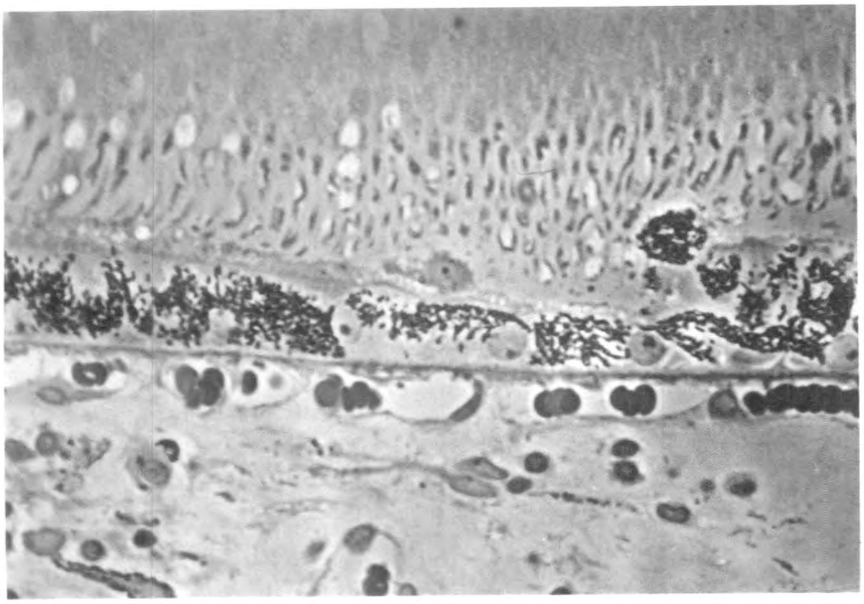

Fig. 5 (Green and Robertson). Higher power light-microscopic view of the transitional zone shown in Figure 4 where the thinned retinal pigment epithelial cells have migrated under the injured retinal pigment epithelial cells (paraphenylenediamine stain, × 1,300).

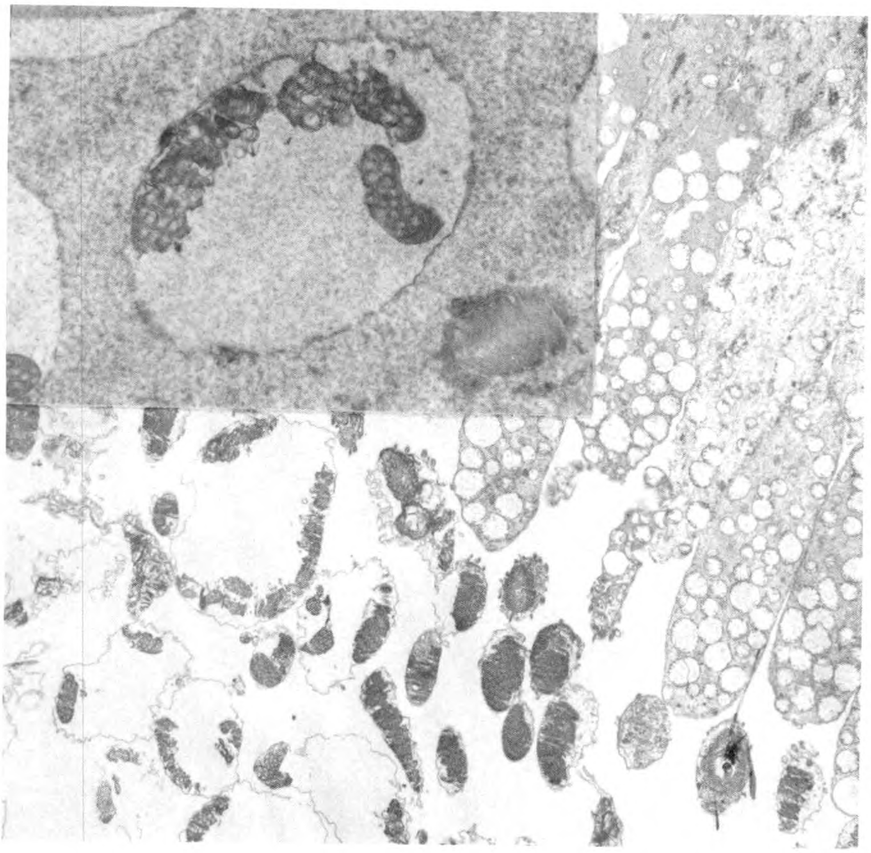

Fig. 6 (Green and Robertson). Electron-microscopic view near the center of the lesion. Extensive derangement of the outer segments of the photoreceptors with distention (main figure), distortion, compaction, partial disintegration of the lamellar disks, and disruption of plasma membranes are apparent. The inner segments of the cones are moderately swollen, and the mitochondria are markedly distended (× 8,500). Inset shows details of the swollen mitochondria (× 2,800; inset, × 8,500).

located at the base of the retinal pigment epithelium (Figs. 7 and 8), where the basement membrane was intact. A few rounded cells without plasma membranes were located internal to the area of the retinal pigment epithelium. Bruch's membrane and the choriocapillaris were intact.

Discussion

This pathologic study demonstrated that in the acute stage of photic retinopathy in human eyes, damage occurs mainly at the level of the retinal pigment epithelium and photoreceptor layer. These findings corroborate the unpublished clinicopathologic study of photic retinopathy in the human eye reported by M. O. M. Tso and D. M. Robertson (presented at the Tenth Annual Scientific Meeting of the Macula Society, Cannes, France, June 27, 1987). Our findings are also consistent with the histopathologic finding of photic retinopathy reported in primates after exposure to light from an operating-room microscope.[7] The relative integrity of the photoreceptor nuclei and some of the inner segments after this relatively severe injury to the pigment epithelium and outer segments of the photoreceptors is not surprising because this injury was only three days old. Although it is possible that degeneration of the photoreceptor cell nuclei might develop later, subhuman primate studies indicate that similarly deranged outer segments of the photoreceptors may be capable of recovery.[7,8]

The microscopic findings seen with photic retinopathy are not greatly dissimilar to the microscopic findings seen in sun-exposed human eyes.[9] In three patients in whom sun gazing was studied, injury to the retinal pigment epithelium was characterized by loss of the pigment granules, migration of the chromatin material, elevation of the necrotic retinal pigment epithelial cells, and sliding of the adjacent normal retinal pigment epithelium under the necrotic cells. The degeneration of the photoreceptor cells after voluntary sun gazing for one hour was mild, partially reversible, observed primarily at the ultrastructural level, and was associated with only a slight decrease in central visual acuity from 20/20 to only 20/25.[9] The

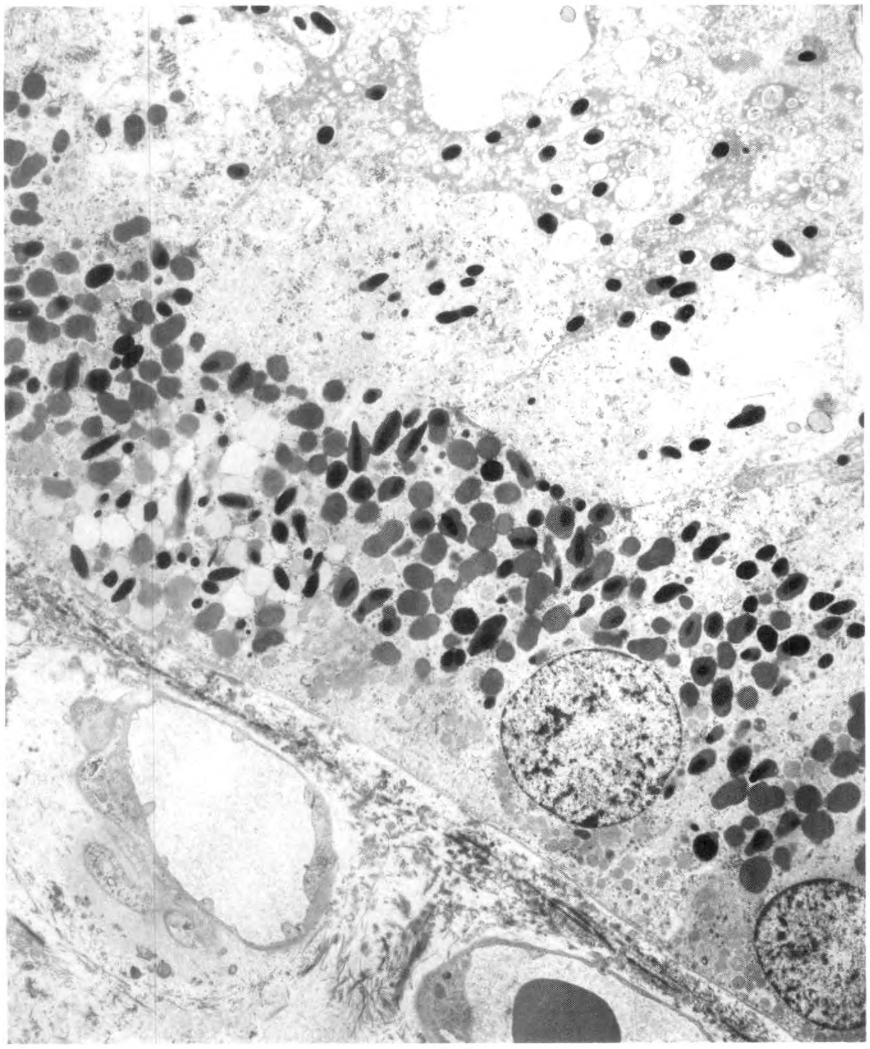

Fig. 7 (Green and Robertson). Electron-microscopic view near center of the lesion. The retinal pigment epithelial cells are severely damaged with loss of plasma membranes, apical villous processes, basal infoldings, and extrusion of pigment granules. Overlying the retinal pigment epithelial cells, a variably dense granular material containing fragments of outer segments is observed (× 2,800).

central visual acuity in this experimental eye with acute photic retinopathy was also only moderately depressed (20/50) and probably was caused by the relative integrity of the inner segments of the photoreceptor cells. Despite the relatively good central visual acuity recorded in this experimental eye, the problem of photic retinopathy caused by ophthalmic instrumentation should not be considered trivial. This experiment was conducted without a retrobulbar anesthetic. In clinical circumstances in which a retrobulbar anesthetic is used, there may be alterations in retinal and choroidal blood flow which may decrease the threshold for light damage. Further, the induction of total akinesia will allow the light energy to be focused on a smaller area of the retina, thus causing the photic injury to be more confined and more severe.

The microscopic findings showed an interesting correlation with the angiographic appearance of photic retinopathy. A central zone of homogeneous hyperfluorescence correlated with the central zone of relatively uniform retinal pigment epithelial cell necrosis. At the perimeter of the photic retinopathy, a hypofluorescent ring that corresponded to the site of a double layer of pigment composed of migrating retinal pigment epithelial cells under necrotic retinal pigment epithelial cells was observed. The peripheral halo of hyperfluorescence corresponded to the thinned relatively depigmented retinal pigment epithelial cells located peripheral to the double layer of retinal pigment

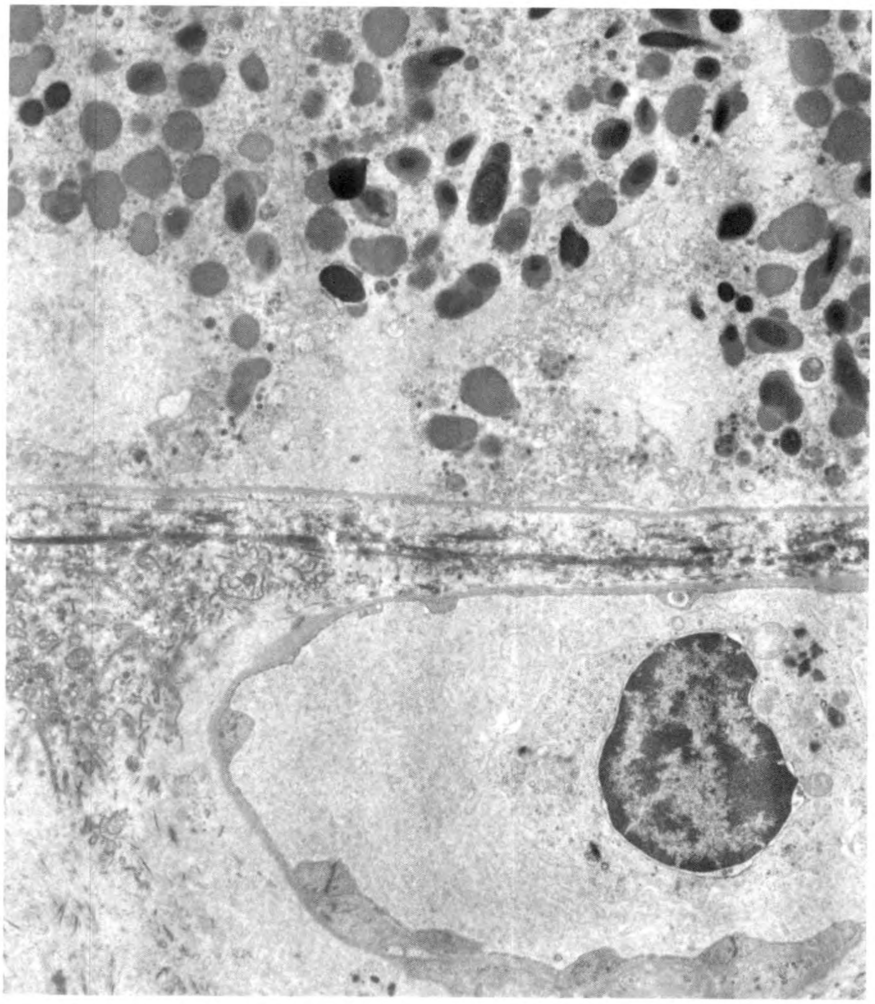

Fig. 8 (Green and Robertson). Electron-microscopic view of necrotic pigment epithelial cells with nuclear chromatolysis and loss of plasma membrane. Bruch's membrane and choriocapillaris appear normal (× 5,400).

epithelial cells. We suggest that these thinned relatively depigmented cells have actively responded in a reparative way and are sliding toward the photic injury. Additionally, the histopathologic finding of a thick central exudate in the outer retina probably correlates with the mother-of-pearl, yellow-white, central macular discoloration seen before enucleation. Because the photic injury was a suprathreshold lesion, we were unable to determine if the macula luteal pigment offered any protection to the underlying photoreceptors and retinal pigment epithelium.

Whereas this clinical pathologic study relates only to the acute stages of photic retinopathy three days after injury, the extent of derangement of the photoreceptors is probably consistent with recovery. Findings of thinned relatively depigmented retinal pigment epithelial cells elevating necrotic pigment epithelial cells suggest a reparative process that has already begun.

References

1. McDonald, H. R., and Irvine, A. R.: Light-induced maculopathy from the operating microscope in extracapsular cataract extraction and intraocular lens implantation. Ophthalmology 90:945, 1983.

2. Boldrey, E. E., Ho, B. T., and Griffith, R. D.: Retinal burns occurring at cataract extraction. Ophthalmology 91:1297, 1984.

3. Ross, W. H.: Light-induced maculopathy. Am. J. Ophthalmol. 98:488, 1984.

4. Khwarg, S. G., Geoghegan, M., and Hanscom, T. A.: Light-induced maculopathy from the operating microscope. Am. J. Ophthalmol. 98:628, 1984.

5. Robertson, D. M., and Feldman, R. B.: Photic retinopathy from the operating room microscope. Am. J. Ophthalmol. 101:561, 1986.

6. Robertson, D. M., and McLaren, J. W.: Photic retinopathy from the operating room microscope. Study with filters. Arch. Ophthalmol. 107:373, 1989.

7. Jaffe, G. J., Irvine, A. R., Wood, I. S., Severinghaus, J. W., Pino, G. R., and Haugen, C.: Retinal phototoxicity from the operating microscope. The role of inspired oxygen. Ophthalmology 95:1130, 1988.

8. Tso, M. O. M., Wallow, I. H. L., Powell, J. O., and Zimmerman, L. E.: Recovery of the rod and cone cells after photic injury. Trans. Am. Acad. Ophthalmol. Otolaryngol. 76:1247, 1972.

9. Tso, M. O. M., and LaPiana, F. G.: The human fovea after sun-gazing. Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:OP-788, 1975.

OPHTHALMIC MINIATURES

James consulted me in April 1871—just as Norton said. He complained of deteriorating vision, combined with watering of the eyes, spasm of the lids and sensitivity to the light. These symptoms were not then well developed, but they were clearly indicative of interstitial keratitis, the commonest cause of which is congenital syphilis.

Robert Goddard, *Painting the Darkness*
New York, Pocket Books, 1989, p. 77

Hydroxychloroquine Retinopathy

Asher Weiner, M.D., Michael A. Sandberg, Ph.D., Alexander R. Gaudio, M.D.,
Mohandas M. Kini, M.D., and Eliot L. Berson, M.D.

We analyzed ocular findings from two patients (aged 49 and 60 years) with hydroxychloroquine (Plaquenil, Winthrop Pharmaceuticals, Division of Sterling Drug, Inc., New York, New York) retinopathy. Both patients were treated for systemic lupus erythematosus; one patient was treated with 400 to 800 mg of hydroxychloroquine per day (6.1 to 12.2 mg/kg of body weight/day) over a ten-year period, whereas the other received 400 mg/day (6.1 mg/kg of body weight/day) over a 20-year period. Cumulative doses were 1,788 and 2,920 g, respectively. Neither patient had ever been treated with chloroquine. One patient complained of glare and difficulty in adjusting to changes in illumination, whereas the other was asymptomatic. Both had bilateral visual acuities of 20/25, pericentral scotomata, and increased final dark-adapted rod thresholds in the two retinal areas that were tested. Full-field electroretinograms were reduced and delayed, and focal cone electroretinography showed abnormal foveal responses as well. Ophthalmoscopy and fluorescein angiography showed a bull's-eye maculopathy in both eyes of one patient and perifoveal depigmentation in both eyes of the other patient. Retinal function remained stable at follow-up examinations 18 to 24 months after the cessation of hydroxychloroquine treatment. These two cases demonstrate that peripheral retinopathy, as well as maculopathy, can develop in patients who are treated with hydroxychloroquine for systemic lupus erythematosus, and that retinal function may remain stable after discontinuation of hydroxychloroquine treatment.

CHLOROQUINE RETINOPATHY was first described in 1959,[1] and many cases have been described since then with abnormal clinical findings, including reduction in visual acuity, a bull's-eye maculopathy, and generalized retinal pigmentary degeneration.[2-9] In contrast, only two unequivocal detailed cases of hydroxychloroquine (Plaquenil) retinopathy have been described in the literature[10,11]; both had normal or reduced visual acuity with pericentral scotomata and a bull's-eye maculopathy. No distinct evidence of generalized retinopathy was observed in these two cases. It has been suggested that patients can tolerate high cumulative doses of hydroxychloroquine with minimal, if any, clinical signs of retinopathy,[11,12] and that there appears to be no upper limit to the total cumulative dose that can be used safely over years, as long as the daily dosage is ≤ 400 mg/day and ≤ 6.5 mg/kg of body weight/day.[11,13] We studied ocular findings in two patients treated with hydroxychloroquine for systemic lupus erythematosus over a period of ten to 20 years; one of them was treated with a daily dose that was within the daily-dosage limits mentioned previously. Neither patient was ever treated with chloroquine.

Case Reports

Case 1

A 49-year-old white woman was referred to the Electroretinography Service of the Massachusetts Eye and Ear Infirmary because of symptoms of glare and difficulty with dark adaptation for nine months. The patient had been treated for systemic lupus erythematosus

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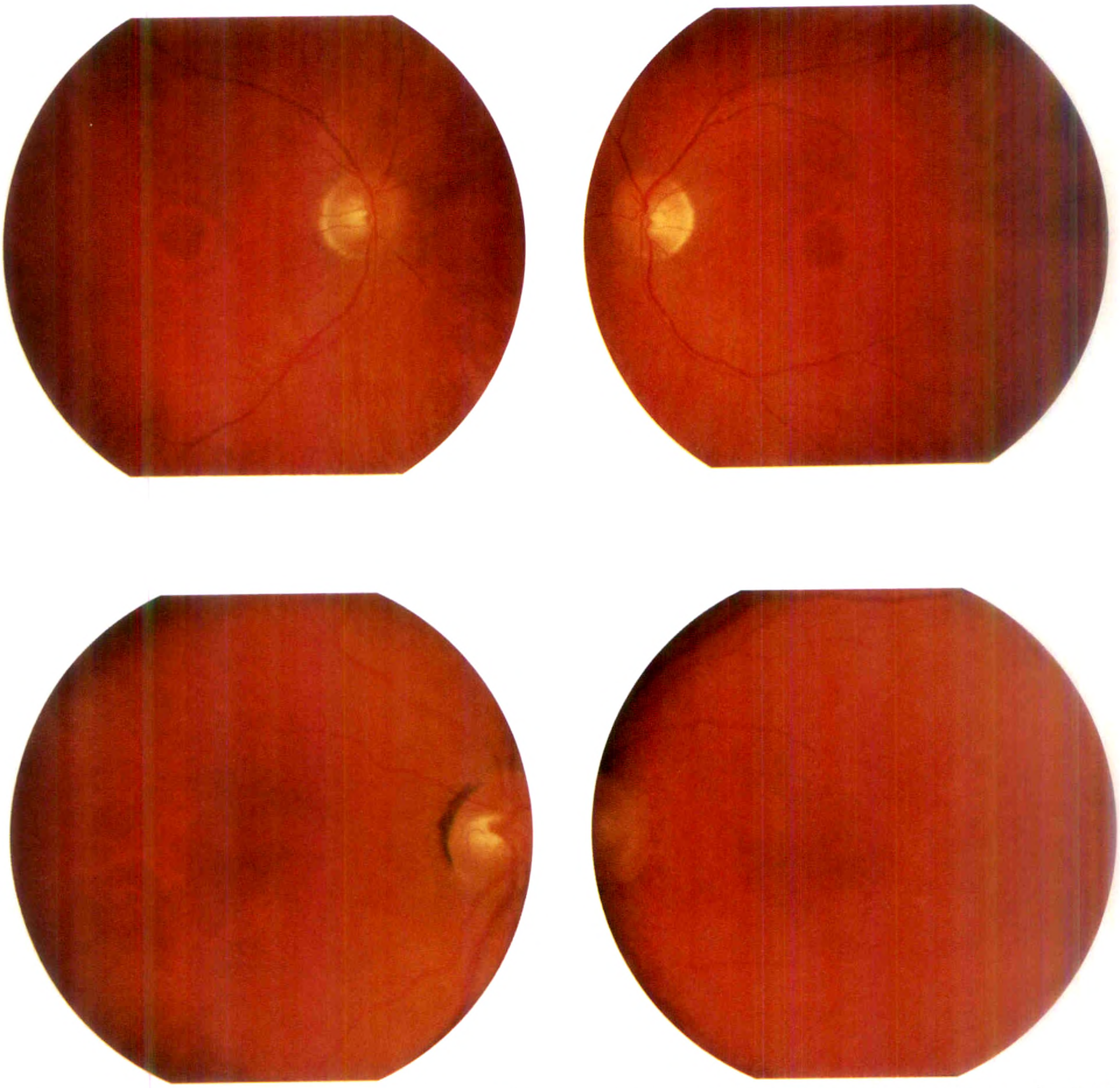

Fig. 1 (Weiner and associates). Top, Case 1. Fundus photographs of right (left) and left (right) eyes of patient with hydroxychloroquine retinopathy. Bottom, Case 2. Fundus photographs of right (left) and left (right) eyes of patient with hydroxychloroquine retinopathy.

over a period of ten years with 400 to 800 mg of hydroxychloroquine per day (6.1 to 12.2 mg/kg of body weight/day); the cumulative dose was 1,788 g. She had also been treated with cortisone but never with chloroquine. No family history of macular degeneration was found. Findings in both eyes included visual acuity of 20/25 with −2.75 sphere, normal intraocular pressures, clear media, normal optic disks, mild retinal arteriolar attenuation, a perifoveal hypopigmented ring surrounded by hyperpigmentation (bull's-eye maculopathy, Fig. 1, top), and mild peripheral retinal pigment epithelial granularity. Pigment epithelial transmission defects were evident on fluorescein angiography, including a perifoveal halo of hyperfluorescence and a punctate pattern in the periphery; neither changed remarkably throughout the transit of dye (Fig. 2, top). Goldmann perimetry showed pericentral scotomata extending out to the 15-degree isopter nasally and to the 50- to 60-degree isopters temporally in both

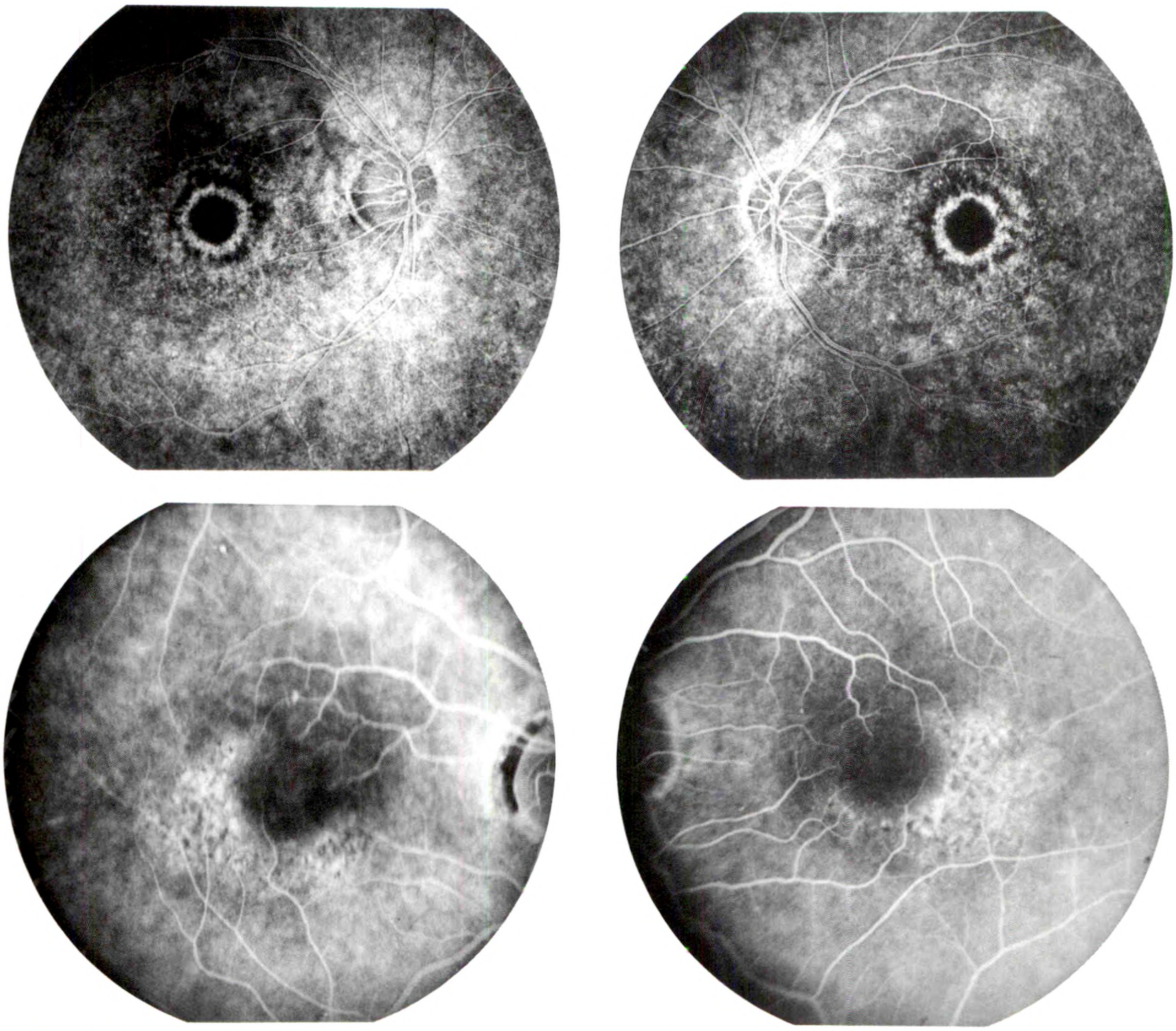

Fig. 2 (Weiner and associates). Top, Case 1. Fluorescein angiograms of right (left) and left (right) eyes of patient with hydroxychloroquine retinopathy. Bottom, Case 2. Fluorescein angiograms of right (left) and left (right) eyes of patient with hydroxychloroquine retinopathy.

eyes (Fig. 3). Bilateral pericentral scotomata were also demonstrated by Amsler grid testing and computerized acuity mapping of the macula[14] (Fig. 4). The patient made eight errors on the Ishihara pseudoisochromatic plates with no specific deficiency but performed normally on the Farnsworth D-15 panel test. Final dark-adapted rod thresholds, measured after 45 minutes of dark adaptation with a Goldmann-Weekers dark adaptometer centrally and 7 degrees above the fovea with an 11-degree white test light, were increased bilaterally 1 log unit above normal.

Full-field electroretinograms, recorded from both eyes as previously described,[15] were abnormal according to the following data (Fig. 5): rod-isolated responses to 0.5-Hz flashes of blue light were undetectable (that is, < 10 μV; normal range for amplitude, 100 to 275 μV); mixed rod and cone responses to 0.5-Hz white light were reduced to 12 μV (normal range, 350 to 700 μV); and cone-isolated responses to 30-Hz white light were reduced to 12 μV (normal range, 50 to 125 μV), and were 36 msec with respect to their implicit times (normal range, 25 to 32 msec).[16] Focal cone electroretinograms, elicited from both eyes with a stimulator-ophthalmoscope,[17] were also abnormal according to the following data (Fig. 5): foveal amplitudes were reduced to 0.10 μV (normal range, 0.18 to 0.55 μV), and parafoveal responses were undetectable (that is, < 0.05 μV; normal range, 0.09

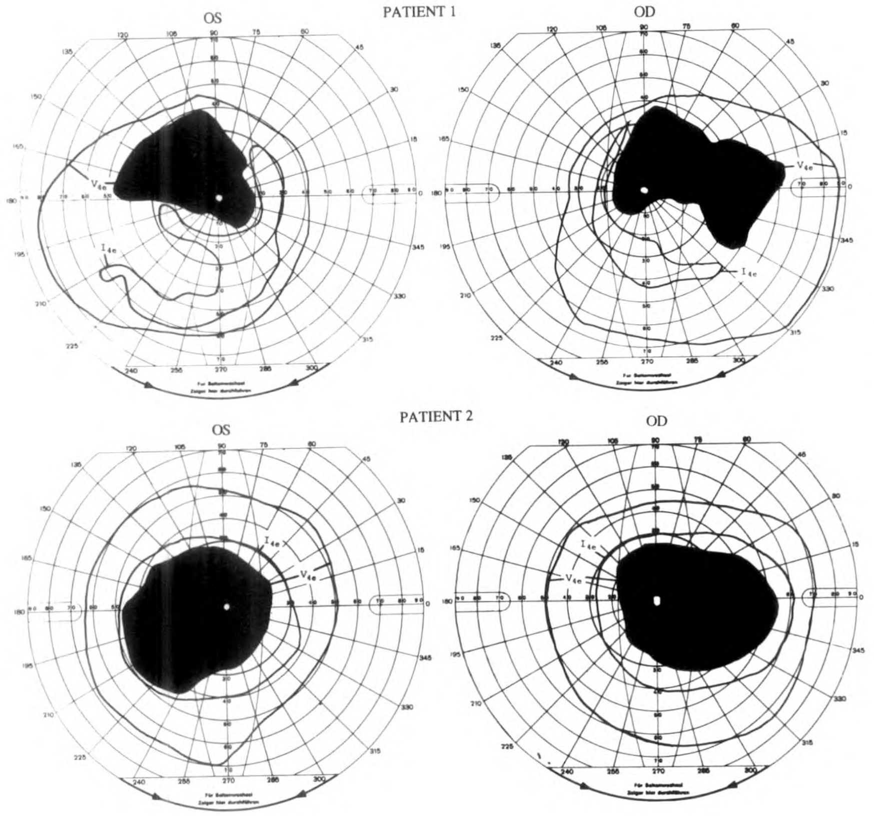

Fig. 3 (Weiner and associates). Top, Case 1. Goldmann visual fields of right (left) and left (right) eyes of patient with hydroxychloroquine retinopathy. Bottom, Case 2. Goldmann visual fields of right (left) and left (right) eyes of patient with hydroxychloroquine retinopathy. Residual central island of vision was 2 to 3 degrees in diameter to the I_{4e} light target in both eyes of both patients.

to 0.27 μV). Hydroxychloroquine treatment was discontinued and a follow-up at six, 12, 19, and 24 months after cessation of treatment disclosed no further visual loss.

Case 2

A 60-year-old white woman being treated with hydroxychloroquine, who failed the Ishihara color plates as a screening test for retinal toxicity, was referred to the Electroretinography Service for retinal examination. She had been treated for systemic lupus erythematosus over a 20-year period with 400 mg of hydroxychloroquine per day (6.1 mg/kg of body weight/day); the cumulative dose was 2,920 g. Aspirin, prednisone, and furosemide had also been prescribed at various times but she had never been treated with chloroquine. No family history of macular degeneration was found. Findings in both eyes included visual acuity of 20/25 with +3.25 sphere, normal intraocular pressures, clear media, normal optic disks, normal retinal arterioles, minimal perifoveal hypopigmentation (more obvious in the right eye than in the left; Fig. 1, bottom), and a normal appearance of the retinal periphery. An incomplete ring-shaped retinal pigment epithelial window defect was evident by fluorescein angiography in both eyes (Fig. 2, bottom). Goldmann perimetry showed bilateral pericentral scotomata extending out to the 20-degree isopter nasally and to the 50-degree isopter temporally (Fig. 3). Pericentral scotomata were also demonstrated by Amsler grid testing and computerized acuity mapping of the macula (Fig. 4). The patient made four errors on the Ishihara pseudoisochromatic plates with no specific deficiency but performed normally on the Farnsworth D-15 panel test. Final dark-adapted rod thresholds were increased 1 log unit above normal centrally and 7 degrees above the fovea in both eyes.

Full-field electroretinograms were abnormal (Fig. 5); rod-isolated responses to 0.5-Hz flashes of blue light were undetectable (that is, < 10 μV), mixed rod and cone responses to 0.5-Hz white light were reduced to 128 μV, and cone-isolated responses to 30-Hz white light were reduced to 41 μV and were 41 msec with respect to their implicit times. Foveal cone electroretinograms were reduced to 0.07 μV (Fig. 5). Hydroxychloroquine treatment was discontinued and a follow-up examination 18 months after cessation of treatment disclosed no further visual loss.

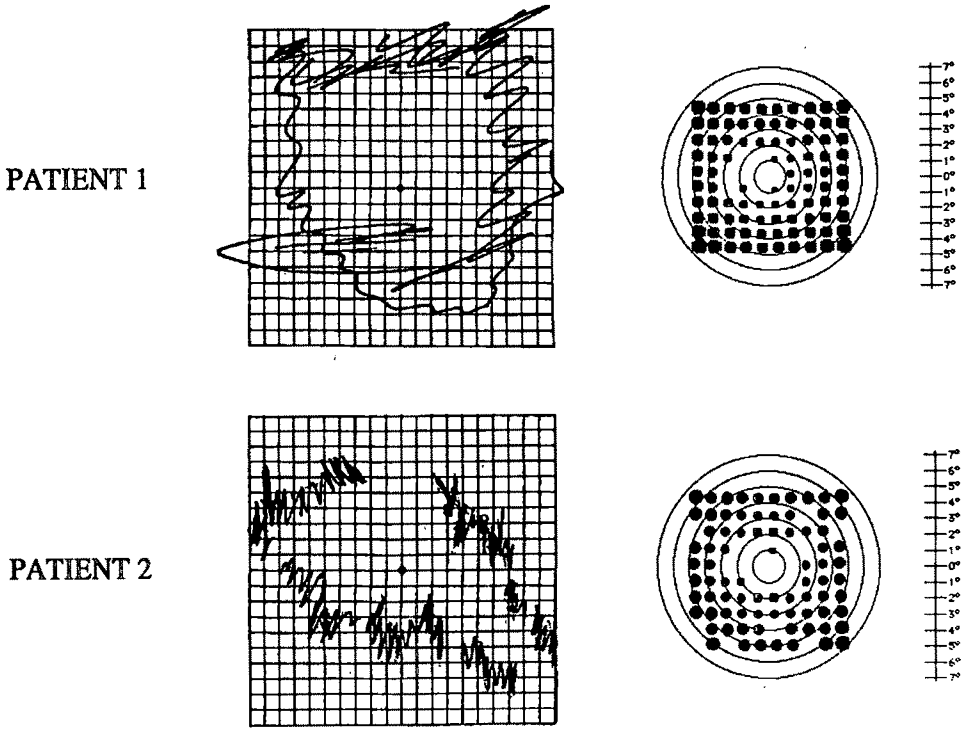

Fig. 4 (Weiner and associates). Top row, Case 1. Amsler grid (left) and computerized acuity mapping of the macula (right). Bottom row, Case 2. Amsler grid (left) and computerized acuity mapping of the macula (right). Hand-drawn lines on Amsler grids represent reported areas of distortion, reduced contrast, or scotomata. Computerized acuity mapping of the macula maps field deficits in the central 10 degrees; it consisted of monocular identification of 100 letters, each flashed separately for a duration of 20 msec in random sequence and location on to a computer screen. The patient fixated a cross in the center of the screen and then pressed a button that caused the letter to be identified to appear on the screen. The letters were scaled in size according to their distance from fixation to compensate for the normal decline in visual acuity with increasing eccentricity from the foveola. Black spots represent missed letters. The upper limits of normal are less than two errors for subjects $<$ 50 years of age and less than five errors for subjects $\geq$ 50 years of age.

Discussion

Our two cases illustrate that hydroxychloroquine can be associated with bilateral retinopathy involving not only the macula but the peripheral retina as well. The maculopathy was evident by the abnormal findings on visual fields and Amsler grid testing, computerized acuity mapping of the macula, focal electroretinography, ophthalmoscopy and fluorescein angiography. The peripheral retinopathy was demonstrated by the scotomata in the midperipheral visual fields and by the markedly reduced and delayed full-field electroretinograms that indicated widespread retinal degeneration, similar to some cases of chloroquine retinopathy previously reported.[4,8] Both patients showed preferential loss of rod function in their full-field electroretinograms. Foveal cone electroretinograms were subnormal in both patients despite central vision that was within the normal range; these amplitude reductions indicated malfunctioning cones within the central macula despite retention of good visual acuity.

In 1967, Shearer and Dubois[10] described a maculopathy in one of 94 patients treated with hydroxychloroquine. The affected patient had received 600 to 1,200 mg of hydroxychloroquine per day (cumulative dose, 770 g), and had reduced visual acuity and a bilateral bull's-eye maculopathy. Johnson and Vine[11] reported another case of hydroxychloroquine maculopathy in 1987. That patient, treated with 500 mg of hydroxychloroquine per day (10.6 mg/kg of body weight/day), had received a cumulative dose of 730 g, and had normal visual acuity, normal color vision, and bilateral pericentral scotomata with a bull's-eye maculopathy. Some published cases of patients with presumed hydroxychloroquine retinopathy were previously treated with chloroquine as well as with

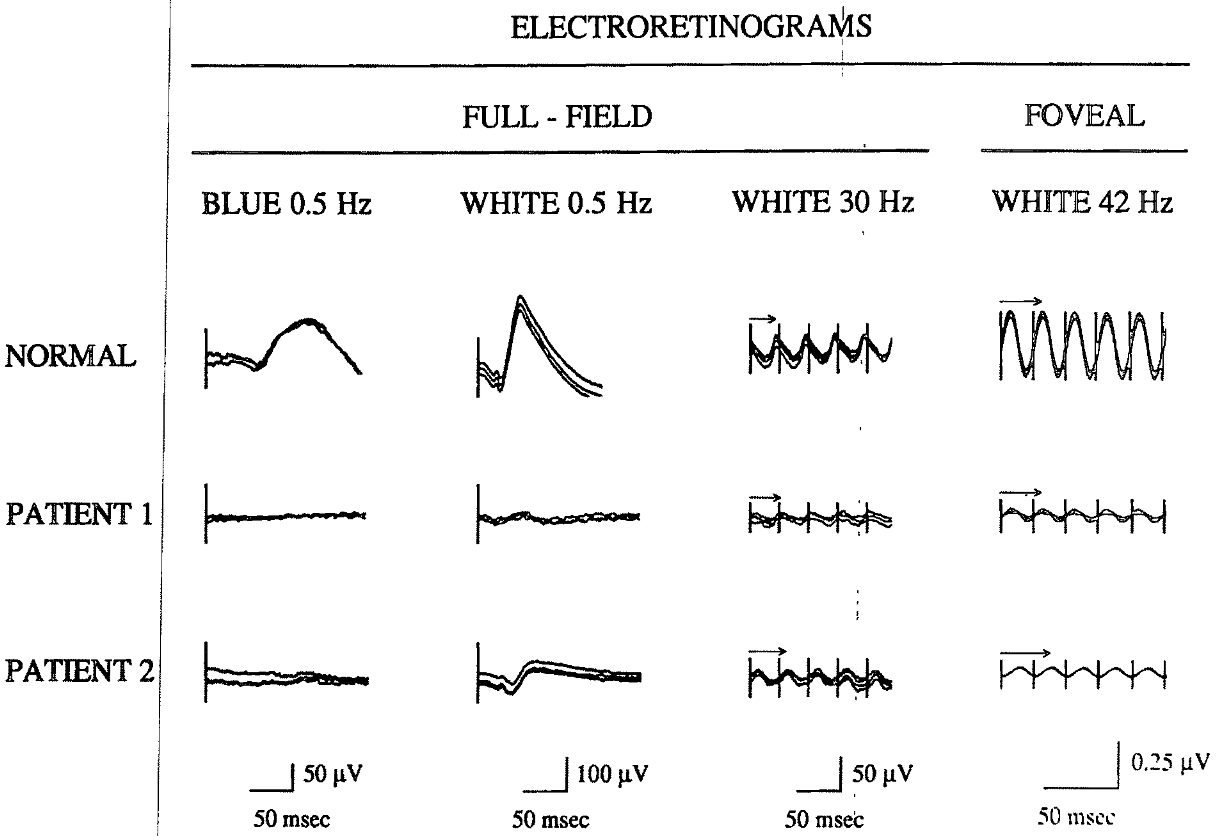

Fig. 5 (Weiner and associates). Full-field electroretinograms (left three columns) and foveal electroretinograms (right column) recorded from a representative normal subject (top row), and from Case 1 (middle row) and Case 2 (bottom row) of hydroxychloroquine retinopathy. For each response, stimulus onset is denoted by vertical lines. Cornea-positivity is an upward deflection. Two or more responses are illustrated for each condition to demonstrate reproducibility. Arrows designate cone b-wave implicit times.

hydroxychloroquine or were reported to have early retinopathy with no marked visual loss.[10-12,18-22] Thus, it is unclear whether these other patients represented true cases of hydroxychloroquine retinopathy. Including the two patients in our study, four unequivocal cases of hydroxychloroquine retinopathy are now described in detail in the literature. The two patients in our study demonstrate that peripheral retinopathy, in addition to maculopathy, can develop in patients treated with this drug.

The mechanism by which hydroxychloroquine could lead to the development of retinopathy is not known. Chloroquine, a closely related compound to hydroxychloroquine by chemical structure,[23] has been shown to have a high affinity for melanin granules,[13] especially in the eye,[24] and to accumulate in the human choroid, ciliary body, and retinal pigment epithelium in proportion to dose and duration of treatment.[25] Additionally, once bound to the tissue, the drug is slowly excreted.[26] Chloroquine may interfere with the function of the retinal pigment epithelium by interfering with cellular processes such as surface-receptor recycling,[27] phagolysosomal digestion,[28] protein synthesis,[26] or metabolism and repair of deoxyribonucleic acid.[29,30] Because the clinical manifestations of the retinopathies associated with chloroquine and hydroxychloroquine appear to be similar, we can speculate that the mechanism for the development of retinopathy is similar for both drugs.

The suggested daily maintenance dose for the treatment of systemic lupus erythematosus has been 200 to 400 mg.[31] It has also been suggested that patients receiving daily dosages of ≤ 400 mg/day (≤ 6.5 mg/kg of body weight/day) may tolerate massive cumulative doses of hydroxychloroquine (for example, 3,923 g) without developing retinopathy.[11,13] However, the second patient in our study was treated with a dosage of 400 mg of hydroxychloroquine per day (6.1 mg/kg of body weight/day), but developed retinopathy, nevertheless.

After discontinuation of hydroxychloroquine treatment, 18 to 24 months of follow-up showed no further visual loss in either patient. Thus, once hydroxychloroquine retinopathy is diagnosed, cessation of hydroxychloroquine treatment may lead to the stabilization of retinal function.

References

1. Hobbs, H. E., Sorsby, A., and Freedman, A.: Retinopathy following chloroquine therapy. Lancet 2:478, 1959.
2. Hobbs, H. E., Eadie, S. P., and Somerville, F.: Ocular lesions after treatment with chloroquine. Br. J. Ophthalmol. 45:284, 1961.
3. Smith, J. L.: Chloroquine macular degeneration. Arch. Ophthalmol. 68:186, 1962.
4. Okun, E., Gouras, P., Bernstein, H., and von Sallmann, L.: Chloroquine retinopathy. A report of eight cases with ERG and dark-adaptation findings. Arch. Ophthalmol. 69:59, 1963.
5. Nozik, R. A., Weinstock, F. J., and Vignos, P. J., Jr.: Ocular complications of chloroquine. A series and case presentation with a simple method for early detection of retinopathy. Am. J. Ophthalmol. 58:774, 1964.
6. Carr, R. E., Gouras, P., and Gunkel, R. D.: Chloroquine retinopathy. Early detection by retinal threshold test. Arch. Ophthalmol. 75:171, 1966.
7. Burns, R. P.: Delayed onset of chloroquine retinopathy. N. Engl. J. Med. 275:693, 1966.
8. Lowes, M.: Peripheral visual field restriction in chloroquine retinopathy. Report of a case. Acta Ophthalmol. 54:819, 1976.
9. Hart, W. M., Jr., Burde, R. M., Johnston, G. P., and Drews, R. C.: Static perimetry in chloroquine retinopathy. Perifoveal patterns of visual field depression. Arch. Ophthalmol. 102:377, 1984.
10. Shearer, R. V., and Dubois, E. L.: Ocular changes induced by long-term hydroxychloroquine (Plaquenil) therapy. Am. J. Ophthalmol. 64:245, 1967.
11. Johnson, M. W., and Vine, A. K.: Hydroxychloroquine therapy in massive total doses without retinal toxicity. Am. J. Ophthalmol. 104:139, 1987.
12. Tobin, D. R., Krohel, G. B., and Rynes, R. I.: Hydroxychloroquine. Seven-year experience. Arch. Ophthalmol. 100:81, 1982.
13. Mackenzie, A. H.: Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. Am. J. Med. 75:40, 1983.
14. Gaudio, A. R., Sandberg, M. A., Miller, S., Kini, M. M., and Berson, E. L.: Computerized acuity mapping of the macula in patients with macular disease. A fixed-criterion test complementary to the Amsler grid. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 690.
15. Berson, E. L., Sandberg, M. A., Maguire, A., Bromley, W. C., and Roderick, T. H.: Electroretinograms in carriers of blue cone monochromatism. Am. J. Ophthalmol. 102:254, 1986.
16. Berson, E. L.: Electroretinographic findings in retinitis pigmentosa. Jpn. J. Ophthalmol. 31:327, 1987.
17. Sandberg, M. A., Jacobson, S. G., and Berson, E. L.: Foveal cone electroretinograms in retinitis pigmentosa and juvenile macular degeneration. Am. J. Ophthalmol. 88:702, 1979.
18. Mills, P. V., Beck, M., and Power, B. J.: Assessment of the retinal toxicity of hydroxychloroquine. Trans. Ophthalmol. Soc. U.K. 101:109, 1981.
19. Easterbrook, M.: The sensitivity of Amsler grid testing in early chloroquine retinopathy. Trans. Ophthalmol. Soc. U.K. 104:204, 1985.
20. Carr, R. E., Henkind, P., Rothfield, N., and Siegel, I. M.: Ocular toxicity of antimalarial drugs. Long-term follow-up. Am. J. Ophthalmol. 66:738, 1968.
21. Crews, S. J.: Chloroquine retinopathy with recovery in early stages. Lancet 2:436, 1964.
22. Adams, E. M., Yocum, D. E., and Bell, C. L.: Hydroxychloroquine in the treatment of rheumatoid arthritis. Am. J. Med. 75:321, 1983.
23. McChesney, E. W., Conway, W. D., Banks, W. F., Jr., Rogers, J. E., amd Shekosky, J. M.: Studies of the metabolism of some compounds of the 4-amino-7-chloroquine series. J. Pharmacol. Exp. Ther. 151:482, 1966.
24. Bernstein, H., Zvaifler, N., Rubin, M., and Mansour, A. M.: The ocular deposition of chloroquine. Invest. Ophthalmol. Vis. Sci. 2:384, 1963.
25. Lawwill, T., Appleton, B., and Altstatt, L.: Chloroquine accumulation in human eyes. Am. J. Ophthalmol. 65:530, 1968.
26. Rubin, M., Bernstein, H. N., and Zvaifler, N. J.: Studies on the pharmacology of chloroquine. Recommendations for the treatment of chloroquine retinopathy. Arch. Ophthalmol. 70:474, 1963.
27. Gonzales-Noriega, A., Grubb, J. H., Talkad, V., and Sly, W. S.: Chloroquine inhibits lysosomal enzyme pinocytosis and enhances lysosomal enzyme secretion by impairing receptor recycling. J. Cell. Biol. 85:839, 1980.
28. Lie, S. O., Schofield, B.: Inactivation of lysosomal function in normal cultured human fibroblasts by chloroquine. Biochem. Pharmacol. 22:3109, 1973.
29. Allison, J. L., O'Brien, R. L., and Hahn, F. E.: DNA. Reaction with chloroquine. Science 149:1111, 1965.
30. Kim, S. H., Kim, J. H., and Fried, J.: Enhancement of the radiation response of cultured tumor cells by chloroquine. Cancer 32:536, 1973.
31. Barnhart, E. R. (ed.): Physicians' Desk Reference, ed. 4. Oradell, New Jersey, Medical Economics Co., Inc., 1991, pp. 2348–2349.

Management of Dislocated Nuclear Fragments After Phacoemulsification

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We examined 13 patients referred for management of dislocated lens fragments after phacoemulsification. Ocular findings included corneal decompensation, glaucoma, inflammation, and retinal tears and detachments. Eleven of the 13 patients underwent vitrectomy with removal of lens fragments. Surgical indications included the presence of large lens fragments, uncontrolled glaucoma, persistent and severe inflammation, and retinal detachment. Better visual acuity was observed in patients who had smaller lens fragments or when vitrectomy was delayed to allow medical treatment of intraocular inflammation and glaucoma. The results indicate that nucleus dislocation during phacoemulsification is an important visual complication, with seven of the 13 patients having a final visual acuity of 20/80 or less.

PHACOEMULSIFICATION and aspiration of cataracts was described by Kelman in the 1960s[1] and then popularized in the 1970s.[2] In 138 cases reported by Fung,[3] the six most frequent complications subsequent to phacoemulsification were permanent corneal edema, disruption of the anterior hyaloid, late opacification of an intact posterior capsule, cystoid macular edema, retinal detachment, and posterior dislocation of the nucleus.

Lens dislocation into the vitreous cavity during an intracapsular cataract operation was recognized as a serious problem.[4] In the 1970s, the incidence of nucleus or fragment dislocation into the vitreous cavity during phacoemulsification was from 0.4% to 4% of patients.[5,6] Recommendations for managing anterior dislocation of the nucleus during phacoemulsification included opening the incision and removing the nucleus with a lens loop. For posterior dislocations of the nucleus, Maloney and Grindle[7] recommended introducing a cyclodialysis spatula through the pars plana, lifting the nucleus from below, and removing it with a lens loop when it was lifted anteriorly. Hutton, Snyder, and Vaiser[8] reported on the use of pars plana vitrectomy to manage lens fragments surgically dislocated into the vitreous cavity. In that study, 19 of 26 patients previously underwent phacoemulsification. Since then few reports have appeared in the literature describing ocular complications associated with posteriorly dislocated nuclei during phacoemulsification.

We examined 13 patients who were referred to our vitreoretinal practice over the past two years, and who had complicated cataract extraction by phacoemulsification associated with partial nucleus dislocation into the vitreous cavity. We discuss management of dislocated lens material during phacoemulsification at the time of the original cataract operation and during subsequent vitreoretinal procedures, as well as indications for a second operation.

Patients and Methods

We studied 13 patients referred to our vitreoretinal practice because of posterior dislocation of lens fragments during phacoemulsification. All patients (five men and eight women; age

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range, 27 to 88 years, with ten who were over 70 years old) were seen within three days of the cataract procedure. Operative findings of the cataract surgeons included ten of 13 patients who had undergone posteriorly directed irrigation to retrieve the dislocated nucleus fragments. None of the surgeons attempted to retrieve the nucleus directly from the vitreous cavity after dislocation. All patients had undergone anterior vitrectomy. The clinical variables evaluated initially and throughout the study included the measurement of visual acuity and intraocular pressure. Inflammation with flare and cell reaction was graded as mild and inflammation with fibrin membrane formation and vitreous haze was graded as moderate. Vitreous hemorrhage was graded as mild when fundus detail was not obscured and was considered moderate when B-scan ultrasonography was necessary to confirm retinal attachment. We estimated the amount and location of residual cortical and nuclear material. The presence and location of intraocular lenses were noted. All patients had complete retinal examinations with scleral depression.

On our first examination of these 13 patients, we observed visual acuities ranging from 20/30 to hand motions with only two patients having a visual acuity of 20/50 or better and 11 with 20/300 or worse. Nine of 13 patients had increased intraocular pressure at initial examination. Vitreous hemorrhaging was observed in seven patients, was mild in two, and moderate in five. Mild intraocular inflammation was observed in all patients and was moderate in five. Corneal findings included seven patients with endothelial striae and four with microcytic edema. Four patients had residual cortex in the anterior chamber at initial examination; ten had residual cortex mixed with nuclear fragments in the posterior cavity. On the basis of clinical examination, we estimated that up to 20% to 80% of the entire nucleus was dislocated posteriorly in all 13 patients, with more than 50% of the nucleus remaining in ten patients. Nine of 13 patients had one nuclear fragment. Four had either two or three at initial examination. All had evidence of microscopic fragments. Six patients had anterior-chamber intraocular lenses; three had posterior-chamber intraocular lenses. We observed no initial retinal tears or retinal detachments.

We initially treated all patients with corticosteroid eyedrops when intraocular inflammation was mild, and with systemic corticosteroids when inflammation was moderate or progressive. Increased intraocular pressure was treated with instillation of eyedrops, and systemic therapy was used when pressure was uncontrolled.

During subsequent follow-up care at intervals ranging from two to 50 days after phacoemulsification, 11 of the 13 patients underwent pars plana vitrectomy with lens removal. Indications for a vitrectomy included the presence of lens fragments; uncontrolled or persistent inflammation, or both; increased intraocular pressure; intolerance to systemic medications; and retinal tears and detachments. In two patients, secondary intraocular lens implantation was recommended to facilitate visual rehabilitation.

General anesthesia was used in all patients undergoing subsequent vitreous and lens operations. Vitrectomies were performed with a standard three-port system. The cataract wound was inspected and reinforced when necessary. If the infusion cannula was not visualized, anterior infusion was performed with a bent 20-gauge needle either in the anterior chamber or through the pars plana. All residual cortical material and hemorrhage were removed from the anterior chambers. Fibrin membranes over the intraocular lenses were peeled with a 25-gauge needle by means of a limbal incision. Vitreous herniation through the capsulotomy or pupil was removed. An anterior vitrectomy was performed early to minimize further vitreous herniation into the anterior chamber. Posterior capsular remnants were removed from eyes with preexisting anterior chamber lenses. Pupillary dilatation was facilitated with the intracameral administration of epinephrine, when necessary. Viscoelastic substances were used to coat the endothelium if residual corneal endothelial striae limited visualization. To prevent vitreous imbrication into the fragmentation tip, anterior and peripheral vitrectomies were performed before posterior fragmentation of nuclear material. Cortical material covering the nucleus was removed with a vitrector. After it was lifted off the retinal surface, the nucleus then was fragmented in the middle of the vitreous cavity. If the nuclear material was difficult to fragment, it was crushed between the light pipe and the vitrector and removed. All residual nuclear particles were removed including fragments at the vitreous base. This process was aided by simultaneous scleral depression. Complete vitrectomy was performed to the level of the vitreous base. At the end of the procedure, indirect ophthalmoscopy and scleral depression were performed to detect retinal tears, which were treated with argon endophotocoagulation. Posterior breaks were not treated with scleral buckles. The use of long-acting gas facilitated retinal tamponade. Patients who developed peripheral breaks had associated scleral-buckling procedures. All patients were monitored for seven months to 2½ years. The same clinical variables were measured as previously described.

Results

Four patients underwent vitrectomy within three days of their initial cataract operation. Progressive inflammation and increased intraocular pressure were observed in two of these patients and an operation by which the lens fragments would be removed and a secondary lens would be implanted to facilitate visual rehabilitation was recommended in the other two patients. Further follow-up of the nine remaining patients disclosed normalization of intraocular pressure with the use of timolol maleate (Timoptic, West Point, Pennsylvania) and acetazolamide (Diamox, Pearl River, New York) in seven patients. Vitreous hemorrhaging resolved within four weeks after initial consultation in all but three patients. Persistent and progressive inflammation including increased corneal striae, moderate anterior uveitis, fibrin membrane formation, and vitreous haze were observed in three patients despite treatment with topical and systemic corticosteroids. Additionally, two of these nine patients developed retinal detachments associated with tears; one developed a tear without detachment within one month of the cataract procedure. Seven of the nine patients underwent vitrectomy with removal of lens fragments from nine to 50 days after the cataract operation. The other two patients responded to treatment and did not require vitrectomy.

Three patients had retinal tears as intraoperative complications and two of these three patients developed intraoperative retinal detachments. Commotio retinae developed in two patients during removal of lens fragments from the retinal surface.

Postvitrectomy follow-up ranged from seven months to 2½ years after the initial nucleus dislocation. Three patients developed chronic glaucoma requiring treatment with topical medication, one of whom required a trabeculectomy. Inflammation resolved after vitrectomy in all patients except Patient 5 who required three weeks of treatment with systemic prednisone. Vitreous hemorrhage resolved in all patients after vitrectomy. Patient 2 developed a moderate recurrence of vitreous hemorrhage three days after vitrectomy, which resolved within one month. Three patients have developed pigment epithelial alterations in the macula relating to contusive damage from the nuclear particles. Four patients (two of whom had iatrogenic breaks) developed detachments after vitrectomy associated with proliferative vitreoretinopathy; one developed a macular pucker without retinal detachment. Two of the four patients who developed detachments underwent further vitrectomy with membrane peeling and scleral buckling with complete reattachment. The macular pucker was peeled without complications. Two patients refused an additional operation despite detachments, which resulted in phthisis bulbi.

Final visual acuities of patients who underwent operations included one patient with 20/30, two with 20/50, one with 20/60, one with 20/80, and one with 20/100. One patient each had 20/150, 20/400, and finger-counting visual acuity (Table). The two patients who refused a subsequent operation after developing redetachment had no light perception. The visual

TABLE

FINAL VISUAL ACUITY RESULTS

	VISUAL ACUITY	
PATIENT	INITIAL	FINAL
1	HM	CF
2	20/200	20/400
3	HM	20/30[*]
4	HM	20/30
5	20/30	20/100
6	20/300	20/150
7	20/400	20/50
8	CF	NLP
9	20/50	20/20[†]
10	HM	20/50
11	HM	NLP
12	CF	20/80
13	20/400	20/60

[*] Did not have vitrectomy.

[†] CF indicates counting fingers, HM indicates hand movement, and NLP indicates no light perception.

acuities of the two patients who did not undergo vitrectomy were 20/20 and 20/30, respectively, after a follow-up of 1½ years. All residual nuclear fragments were resorbed.

Discussion

One study has discussed nucleus dislocation into the vitreous cavity during different types of cataract operations and the management of its subsequent problems (Blodi, B.A., Flynn, H.W., Blodi, C.F., Folk, J.C., and Daily, M.J., poster, Annual Meeting of the American Academy of Ophthalmology, Atlanta, Georgia, Oct. 28–Nov. 1, 1990). In our study, we examined and treated 13 patients who had nucleus dislocation into the vitreous cavity during phacoemulsification.

No definitive guidelines and recommendations have been established for surgical intervention in the management of dislocated lens fragments after phacoemulsification. Our evolving indications for vitrectomy included facilitating visual rehabilitation by removal of large lens fragments (and simultaneous implantation of intraocular lens in two patients). Additional indications for vitrectomy included persistent or uncontrolled glaucoma or inflammation, or both; intolerance or long-term use of systemic medications; and retinal detachments.

Inflammation and vitreous hemorrhage were marked in three of the four patients whose intraocular pressure could not be controlled despite systemic and topical therapy. These exacerbating factors may be related to the extent of manipulation attempted at the time of the cataract operation. Progressive inflammation was more common in patients who initially had cortical material in both the anterior chamber and in the posterior vitreous admixed with posterior nuclear fragments. This finding is consistent with Chandler's observation[9] that the cortical material is mostly responsible for the uveitis that develops from complicated cataract procedures. The inflammatory response of Patient 5 was atypical because it was delayed and because hypopyon accumulation developed five weeks after the cataract operation. Vitrectomy was indicated to rule out endophthalmitis. No organisms were cultured. Although cytology was not performed, the clinical course was similar to one reported by Smith and Weiner[10] as phacoanaphylactic endophthalmitis after phacoemulsification.

In 1978, Wilkinson, Anderson, and Little[11] reported a 3.6% incidence (54 of 1,500 patients) of retinal detachment in patients who underwent phacoemulsification. The risk of detachment increased to 14% with vitreous loss. Our results of two of 13 eyes (15.3%) developing detachments is similar to that of Hutton, Snyder, and Vaiser[8] who reported two of 19 eyes (10.5%) with retinal detachments after nucleus loss associated with phacoemulsification. The retinal tears and detachments that developed may be related to a number of factors including the nuclear particle itself directly tearing the retina, the loss of vitreous, and the degree of manipulation during phacoemulsification. Hemorrhaging, inflammatory products, and retained nuclear fragments also may exacerbate vitreoretinal traction resulting in detachment.

In our study of patients who underwent operations for nucleus dislocation, seven of 11 patients (63%) developed 20/200 or better final visual acuities (Table). These results correlate with those of Blodi and associates, who found that 23 of 36 of patients (63%) who underwent an operation developed visual acuities of 20/200 or better. Because our study was small, conclusions must be drawn with caution. We did observe that final visual acuities in both nonvitrectomized and vitrectomized eyes tended to be better in patients with smaller dislocated nuclear fragments. Furthermore, our results suggested that eyes not requiring emergent vitrectomy may achieve better visual acuity. Of the four eyes that underwent vitrectomy within three days after cataract operations, two had final visual acuities of 20/80 and 20/400, and two had no light perception. This group included the two patients who developed iatrogenic retinal breaks and subsequent proliferative vitreoretinopathy. When vitrectomy was performed between nine and 50 days after the initial operation, better visual acuities resulted. Many factors may account for these differences and further study is warranted. Because seven of the 13 patients in our study (54%) had final visual acuities of 20/80 or less, lens dislocation during phacoemulsification should be considered a potentially important visual complication.

Of the three patients in our study who developed chronic glaucoma, two had undergone delayed vitrectomy (35 to 50 days), a finding consistent with Blodi and associates' report that a higher incidence of chronic glaucoma develops in patients undergoing vitrectomy three weeks after initial lens dislocation.

As phacoemulsification becomes more popular, we expect that more complications, particularly nucleus dislocation, will be reported. In our study, we could not determine specifically whether some of the complications that developed were directly related to attempts by the cataract surgeon to retrieve the nucleus. We generally recommend that these attempts be minimized. If the nucleus is dislocated anteriorly and is visualized, removal by irrigation or a lens loop can be attempted. Once the nucleus has been dislocated beyond the posterior chamber, the operation should be terminated. Further attempts may increase vitreous loss resulting in vitreous hemorrhages, tears, and primary retinal detachments. The removal of residual cortical material, anterior vitrectomy, and prompt use of local and systemic medical management may minimize inflammation and decrease intraocular pressure. Residual posterior capsule remnants should be left intact to facilitate future posterior-chamber lens implantation if indicated. The presence of an intraocular lens can make a nucleus removal more difficult; however, there are no absolute contraindications to its original placement. In this study, we encountered no technical difficulties removing retained nuclei in the presence of anterior and posterior chamber lenses. Relative contraindications for lens implantation include marked corneal decompensation or complete dislocation of a hard nucleus, which may need to be removed through a limbal incision. Early vitreoretinal consultation is recommended.[3,7,12]

The results of this study suggest that patients with nuclear fragments after phacoemulsification be initially monitored, thus allowing ocular stabilization and perhaps obviating the need for an operation or facilitating an operation by enhancing corneal clarity. Additionally, this delay may reduce subsequent intra- or postoperative bleeding and facilitate hydration and removal of the nuclear fragments. If intraocular inflammation or secondary glaucoma cannot be controlled medically or retinal tears and detachments develop, an emergent operation is recommended. Although we proceeded with the operation in most cases on the basis of the considerable size of the nuclei, as did Blodi and associates, we are not certain if this approach is correct. Machemer[13] reported that lens nuclei may be well tolerated within the vitreous cavity in a vitrectomized eye. Perhaps conservative management can be considered in patients with large nuclear fragments in the absence of notable cortex, increased intraocular pressure, and inflammation. A large series of patients should be examined to determine if an operation or its timing affects its facility and the development of chronic complications including glaucoma, cystoid macular edema, and retinal detachment.

References

1. Kelman, C. D.: Phaco-emulsification and aspiration. A new technique of cataract removal. A preliminary report. Am. J. Ophthalmol. 64:23, 1967.
2. Kelman, C. D.: Phaco-emulsification and aspiration. A report of 500 consecutive cases. Am. J. Ophthalmol. 75:764, 1973.
3. Fung, W. L.: Phacoemulsification. Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:46, 1978.
4. Hughes, W. F., Jr., and Owen, W. C.: Postoperative complications of cataract extraction. Arch. Ophthalmol. 38:577, 1947.
5. Cotlier, E., and Rose, M.: Cataract extraction by the intracapsular methods and by phacoemulsification. The results of surgeons in training. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:163, 1976.
6. Heurite, F. G.: The contraindications to phacoemulsification. In summary, a personal experience. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78:14, 1974.
7. Maloney, W. F., and Grindle, L.: Text Book of Phacoemulsification. Fallbrook, California, Lasenda Publishers, 1988, pp. 121–122.
8. Hutton, W. L., Snyder, W. B., and Vaiser, A.: Management of surgically dislocated intravitreal lens fragments by pars plana vitrectomy. Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:176, 1978.
9. Chandler, P. A.: Problems in the diagnosis and treatment of lens induced uveitis and glaucoma. Arch. Ophthalmol. 60:828, 1958.
10. Smith, R. E., and Weiner, P.: Unusual presentation of phacoanaphylaxis following phacoemulsification. Ophthalmic Surg. 7:65, 1976.
11. Wilkinson, C. P., Anderson, C. S., and Little, J. H.: Retinal detachment following phacoemulsification. Ophthalmology 85:151, 1978.
12. Michels, R. J., and Shacklet, T. D. E.: Vitrectomy techniques for removal of retained lens material. Arch. Ophthalmol. 95:1767, 1977.
13. Machemer, R.: A new concept for vitreous surgery. 2. Surgical technique and complications. Am. J. Ophthalmol. 74:1022, 1972.

Recurrent Idiopathic Lateral Rectus Muscle Palsy in Adults

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Recurrent, unilateral, isolated, idiopathic lateral rectus muscle palsy is an uncommon but well-recognized disorder in children that has not been recognized as well in other age groups. We studied five cases of this uncommon entity that we encountered in adults and adolescents. Ages at onset ranged from 15 to 72 years and there were three to eight episodes per patient. Most of the patients shared the following features with the previously reported pediatric cases: ipsilateral recurrence, lack of pain, spontaneous recovery within six months, and no clear cause. Unlike the children, females or left-eye involvement was not preponderant in adults.

BARNETT FIRST REPORTED recurrent isolated lateral rectus muscle palsies in children in 1972 and characterized the disorder as benign and cryptogenic.[1] Despite the larger number of adults with lateral rectus muscle palsies, the frequency and clinical features of recurrent palsies have not been as frequently documented in the nonpediatric age group. We encountered five such cases in adults and adolescents between 1966 and 1990 in a neuro-ophthalmic consultation practice. They represent 1.6% of the 316 outpatients with isolated lateral rectus muscle palsies examined during that 24-year period.

Case Reports

Case 1

A 28-year-old healthy man developed a painless, right lateral rectus muscle palsy shortly after eating turkey in 1980. Complete neurologic and ophthalmologic examinations showed no other abnormalities and results of a glucose tolerance test were normal. Recovery was spontaneous and complete in several months. Immediately after the next time he ate turkey he suffered an identical attack. Results of computed tomography of the head with contrast, visual and brainstem auditory-evoked responses, and an intravenous edrophonium chloride test were all negative. The only abnormal finding on examination of the cerebrospinal fluid was 16 lymphocytes per cubic mm with a normal IgG concentration. He recovered in about six weeks but had five more episodes of isolated, painless, self-limited, right lateral rectus muscle palsy over the next two years. Because three of the episodes occurred after the consumption of turkey, a physician implicated turkey allergy and instituted an extensive investigation. However, when the four subsequent episodes occurred despite scrupulous avoidance of turkey, this theory was dropped.

Case 2

A 15-year-old healthy boy developed horizontal diplopia in 1982, which he could ameliorate by turning his head to the right. No pain or other symptoms were observed. Complete neurologic and ophthalmologic examinations disclosed only a right lateral rectus muscle palsy. No special tests were performed and he recovered completely and spontaneously within weeks. However, identical episodes occurred in each of the two subsequent years. During the third episode, computed tomography of the head with contrast showed no abnormalities. During a fourth attack at the age of 20 years, he underwent cerebral angiography, the results of which were negative. Eighteen months later, he suffered his fifth self-limited right lateral rectus muscle palsy. It was identical to the others except that a slight headache, neckache, and backache without fever accompanied the diplopia at onset. Intravenous administration of edrophonium chloride did not improve his ocular motility.

Case 3

A 44-year-old healthy man developed horizontal diplopia that was worse on left gaze in 1977. No pain or other symptoms were observed. Complete ocular and neurologic examinations showed only a left lateral rectus muscle

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palsy and he was admitted to a hospital for further investigation. Cerebral angiography, computed tomography of the head with contrast, examination of his cerebrospinal fluid (no oligoclonal bands), and various blood tests gave unremarkable results. He recovered completely and spontaneously in three months. However, there were identical recurrences at the ages of 46, 54, and 56 years. Acetylcholine receptor antibodies and Lyme titers were negative, and results of magnetic resonance imaging of the brain with gadolinium were normal.

Case 4

A 16-year-old girl developed horizontal diplopia without pain or other symptoms in 1984. When she was an infant her parents had been concerned that she had strabismus but an ophthalmologist who examined her at that time found normal ocular motility. Her general health was good. Ophthalmic and neurologic examinations showed only a left lateral rectus muscle palsy. Special investigations and treatment were not instituted and she recovered fully within two months. She then remained well until the age of 21 years, when she developed painless diplopia on left gaze. Examination showed only that the left lateral rectus muscle palsy had recurred. Visual and brainstem auditory-evoked responses, acetylcholine receptor antibodies, and results of magnetic resonance imaging were negative. She improved without treatment in three months and horizontal diplopia only on extreme left gaze remained. At the age of 22 years, she had her third attack of a self-limited left lateral rectus muscle palsy. Results of neurologic examination and magnetic resonance imaging were negative.

Case 5

A 72-year-old healthy woman developed horizontal binocular diplopia in 1974 two weeks after having an upper respiratory tract infection with fever. Pain or other symptoms were not observed. Her diplopia disappeared in two weeks and she was well for a year when she again developed painless, horizontal binocular diplopia shortly after having an upper respiratory tract infection with fever. Examination showed only a left lateral rectus muscle palsy. A glucose tolerance test gave normal results. It took three months for the palsy to recover. However, one year later the painless, left lateral rectus muscle palsy recurred. Neuro-ophthalmologic examination was otherwise unremarkable. Plain cranial radiographs were unremarkable and she recovered in two weeks. Polymyalgia rheumatica was diagnosed at the age of 76 years and treated with orally administered prednisone, but she had at least five more identical episodes of ophthalmoparesis. She resides in a nursing home at the age of 91 years without neurologic deficit or ophthalmoparesis and has not complained of diplopia since a disciform macula hemorrhage effectively blinded her right eye four years earlier.

Discussion

The clinical profiles and probable causes of lateral rectus muscle palsies in all age groups were reported in three large studies of Mayo Clinic patients with third, fourth, and sixth cranial nerve palsies.[2-4] Most patients with extraocular muscle palsies were adult, because 90% of the patients in the 1981 series were older than 19 years of age. A cause was not established in 29.6% of the cases of lateral rectus muscle palsies. This figure is surprisingly unchanged from the 1958 Mayo Clinic study despite the availability of computed tomography in the more recent study. Although half of the patients were said to have recovered, information on recurrences was not provided. Shrader and Schlezinger[5] studied 104 patients with isolated sixth-nerve palsies in 1960. Almost 70% were over 50 years old and 24% were idiopathic. The only recurrences were in patients known to have multiple sclerosis. Judging from our experience and the dearth of reported cases, recurrent isolated idiopathic lateral rectus muscle palsies must be uncommon.

The literature on recurrent isolated lateral rectus muscle palsies is mostly pediatric. Five years after Knox, Clark, and Schuster[6] described painless, benign, lateral rectus muscle palsies after febrile illnesses in children, Barnett[1] showed that these isolated lateral rectus muscle palsies can recur. This was supported by later reports of similar cases after viral illnesses or immunization.[7-9] As early as 1975 Scharf and Zonis[10] noted that recurrent isolated lateral rectus muscle palsies could also occur in healthy children without an antecedent viral illness. On the basis of the three largest and most recent studies,[11-13] spontaneous recovery within six months in most patients, ipsilateral recurrence, lack of pain, inability to establish a cause, and a preponderance of females and left-sided palsies are evident. Recurrent lateral rectus muscle palsies represented 4% of 131 patients with lateral rectus muscle palsies under 18 years of age examined during 22 years at one center.[13] Our patients resemble the pediatric patients in that recurrences were ipsilateral, painless, and tended to recover spontaneously in six months or less. However, unlike the pediatric patients, females and left-sided palsies were not preponderant. In fact, three of our five patients were male.

It is likely that the lesions responsible for the recurrent lateral rectus muscle palsies in our patients were extramedullary because they were all isolated deficits, although a few cases of isolated abducens palsy without a conjugate gaze palsy have recently been described from intrapontine lesions involving the abducens fasciculus on magnetic resonance imaging or computed tomography.[14-16] The lack of clinical or radiographic orbital signs suggests an intracranial localization. Although the patients probably had extramedullary intracranial sixth-nerve lesions, it is impossible to determine where or how the lesions developed. Neither myasthenia gravis nor multiple sclerosis, diseases in which spontaneously remitting recurrent ophthalmoplegia can occur, can be confidently excluded. However, myasthenia seems unlikely without eyelid or systemic involvement and because of negative test results in four of the five patients. Multiple sclerosis also seems unlikely because of the lack of any other clinical manifestations during a follow-up interval of four to 17 years. One patient was 72 years old when she had her first episode, which would be extraordinarily late for the onset of multiple sclerosis. Plaques were not seen on the magnetic resonance imaging scans of the two patients who were scanned.

Afifi and associates[13] have hypothesized that once the sixth nerve has been damaged by trauma or infection, the threshold to further damage is lowered. In our patients there was evidence for an initiating injury in only one patient with a viral prodrome. In one other patient a spinal fluid pleocytosis suggested that the sixth nerve in the subarachnoid space might be inflamed. Juncos and Beal[17] described a mild pleocytosis in patients with idiopathic cranial polyneuropathy and retro-orbital pain, most frequently involving the sixth nerve. Self-limited lateral rectus muscle palsy was evident in these cases. Although recurrences were reported, none were limited to a single cranial nerve.

In our experience, the palsy does not tend to become permanent despite multiple recurrences. Isolated recurrent lateral rectus muscle palsies in both children and adults in most cases are self-limited and benign.

References

1. Barnett, A. M.: Benign recurrent abducens palsy in children. S. Afr. Med. J. 46:1662, 1972.
2. Rucker, C. W.: Paralysis of the third, fourth, and sixth cranial nerves. Am. J. Ophthalmol. 46:787, 1958.
3. ———: The causes of paralysis of the third, fourth, and sixth cranial nerves. Am. J. Ophthalmol. 61:1293, 1966.
4. Rush, J. A., and Younge, B. R.: Paralysis of cranial nerves III, IV, and VI. Arch. Ophthalmol. 99:76, 1981.
5. Shrader, E. C., and Schlezinger, N. S.: Neuro-ophthalmologic evaluation of abducens nerve paralysis. Arch. Ophthalmol. 63:84, 1960.
6. Knox, D. L., Clark, D. B., and Schuster, F. F.: Benign VI nerve palsies in children. Pediatrics 40:560, 1967.
7. Sternberg, I., Ronen, S., and Arnon, N.: Recurrent, isolated, post-febrile abducens nerve palsy. J. Pediatr. Ophthalmol. Strabismus 17:323, 1980.
8. Bixenman, W. W., and von Noorden, G. K.: Benign recurrent VI nerve palsy in childhood. J. Pediatr. Ophthalmol. Strabismus 18:29, 1981.
9. Werner, D. B., Savino, P. J., and Schatz, N. J.: Benign recurrent sixth nerve palsies in childhood secondary to immunization or viral illness. Arch Ophthalmol. 101:607, 1983.
10. Scharf, J., and Zonis, S.: Benign abducens nerve palsy in children. J. Pediatr. Ophthalmol. 12:165, 1975.
11. Reinecke, R. D., and Thompson, W. E.: Childhood recurrent idiopathic paralysis of the lateral rectus. Ann. Ophthalmol. 13:1037, 1981.
12. Boger, W. P., Puliafito, C. A., Magoon, E. H., Sydnor, C. F., Knupp, J. A., and Buckley, E. G.: Recurrent isolated sixth nerve palsy in children. Ann. Ophthalmol. 16:237, 1984.
13. Afifi, A. K., Bell, W. E., Bale, J. F., and Thompson, H. S.: Recurrent lateral rectus palsy in childhood. Pediatr. Neurol. 6:315, 1990.
14. Donaldson, D., and Rosenberg, N. L.: Infarction of abducens nerve fascicle as a cause of isolated sixth nerve palsy related to hypertension. Neurology 38:1654, 1988.
15. Johnson, L. N., and Hepler, R. S.: Isolated abducens nerve paresis from intrapontine, fascicular abducens nerve injury. Am. J. Ophthalmol. 108:459, 1989.
16. Bronstein, A. M., Morris, J., Du Boulay, G., Gresty, M. A., and Rudge, P.: Abnormalities of horizontal gaze. Clinical, oculographic and magnetic resonance imaging findings. I. Abducens palsy. J. Neurol. Neurosurg. Psychiatry 53:194, 1990.
17. Juncos, J. L., and Beal, M. F.: Idiopathic cranial polyneuropathy. Brain 110:197, 1987.

Treatment of Infectious Scleritis and Keratoscleritis

Mike G. Reynolds, M.D., and Eduardo Alfonso, M.D.

We reviewed 28 cases of culture-proven infectious scleritis and keratoscleritis to clarify the role of an operation in this disorder. Surgical management in 11 patients with keratoscleritis included cryotherapy, five; penetrating corneal-scleral graft, two; lamellar corneoscleral graft, two; and tectonic penetrating keratoplasty, two; in addition to intensive fortified antibiotic eyedrops. Eight patients with keratoscleritis were treated medically only with intensive fortified frequent antibiotic eyedrops, one; intensive instilled plus intravenous antibiotics, three; and instilled, intravenous, and subconjunctival antibiotics, four. Seven of eight patients treated with antibiotics alone and two of 11 patients who received surgical intervention in addition to antibiotics eventually required evisceration or enucleation of the eye. These results suggest that cryotherapy, lamellar or penetrating corneoscleral graft, in addition to intensive antibiotic therapy, may improve the outcome of patients with infectious keratoscleritis. Five eyes with isolated scleritis without corneal involvement were treated with conjunctival recession and cryotherapy in addition to aggressive antibiotics, and four were treated with antibiotics alone. The infections of these nine patients resolved.

INFECTIOUS SCLERITIS either alone or in combination with keratitis is difficult to manage. Previous reports have emphasized the generally poor outcome of patients with infectious keratoscleritis who were managed with antibiotics alone.[1-3] Some investigators have suggested that cryotherapy or corneal transplantation, or both, in conjunction with antibiotics may improve the outcome in these patients.[4] We reviewed a series of 28 patients with culture-proven infectious scleritis and keratoscleritis seen at our institution to clarify the role of an operation in this disorder.

Patients and Methods

We reviewed the medical records of patients with culture-proven infectious scleritis or keratoscleritis at our institution from August 1981 to May 1989. Cultures had been obtained by previously described standard methods.[5] The cases associated with infected scleral buckle elements were excluded. Twenty-eight patients met this clinical criteria. Nineteen patients had corneal and scleral involvement or keratoscleritis; and nine patients had scleral involvement alone.

For the cases of keratoscleritis, the area of corneal involvement was estimated by reviewing photographs or pictures drawn by the senior staff at the time of the patient's initial examination, or both. The area of involvement was estimated to the nearest one eighth (12.5%) of the total corneal area. The average percentage of corneal involvement was 45% with a range of 12.5% to 100%. Similarly, the degree of scleral involvement was estimated to the nearest clock hour. The average degree of scleral involvement was 4.5 clock hours with a range of 1 to 12 clock hours.

Results

The average age of the patients was 72 years with a range of 36 to 89 years. There were 14 men and 14 women. Risk factors included the following: (1) contact-lens wear, one; (2) neovascular glaucoma, four; (3) AIDS, one; (4) a recent ocular operation, five; (5) recent suture

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removal, two; (6) pterygium removal, four; (7) phacomorphic glaucoma, two; and (8) use of topical eye medications, 22; with 14 of these 22 using corticosteroid eyedrops.

The involved eyes of 20 patients had previously been operated on. Five of these eyes were operated on within two months of the onset of the infection. Of these five, two were operated on for cataract, two had wound dehiscence and resuturing of a corneal graft, and a trabeculectomy was performed on one. Two patients had suture removal within three weeks of their initial examination. Four patients had pterygium removal years before, and three of these were subsequently treated with beta irradiation of the involved sclera.

Twenty-two patients were using topically applied and instilled eye medication in the affected eye at the time of initial examination. Of these 22 patients, 14 were using topically applied corticosteroids, and one was using proparacaine eyedrops, which had been prescribed by another practitioner for a corneal abrasion. One of the patients was using timolol, which was culture-positive for *Pseudomonas* organisms. None of the other topically applied or instilled medications was cultured. The 19 patients with keratoscleritis had various degrees of involvement of the cornea with extension into the sclera (Fig. 1). The area of involvement in nine patients with scleral involvement alone ranged from a small area secondary to a stitch abscess to more extensive areas of involvement (Fig. 2).

Pseudomonas aeruginosa was the responsible organism in 20 patients. However, *Pseudomonas* organisms were responsible in 16 of our 19 cases of keratoscleritis and accounted for only four of the nine cases of isolated scleritis. *Streptococcus pneumoniae*, fungus *Acremonium*, and *Mycobacterium chelonei* each accounted for one case of keratoscleritis. *Staphylococcus epidermidis* accounted for two cases of isolated scleritis and *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Mycobacterium tuberculosis* organisms each accounted for one case.

All patients were treated every 30 minutes to one hour with fortified antibiotic eyedrops. Initially, patients were treated with an aminoglycoside (tobramycin or gentamicin) in addition to an antibiotic for gram-positive coverage (cefazolin or vancomycin), unless the infecting organism was known at the time of initial examination. All the *Pseudomonas* organisms were sensitive (minimal inhibitory concentration or Kirby-Bauer disk diffusion method, or both) to tobramycin, and all except one were sensitive to gentamicin, and this particular patient had been treated with tobramycin initially. The treatment of one patient was changed to amikacin because the sensitivity of the *Pseudomonas* species responsible for the patient's keratoscleritis was intermediately sensitive to tobramycin and gentamicin, but was highly

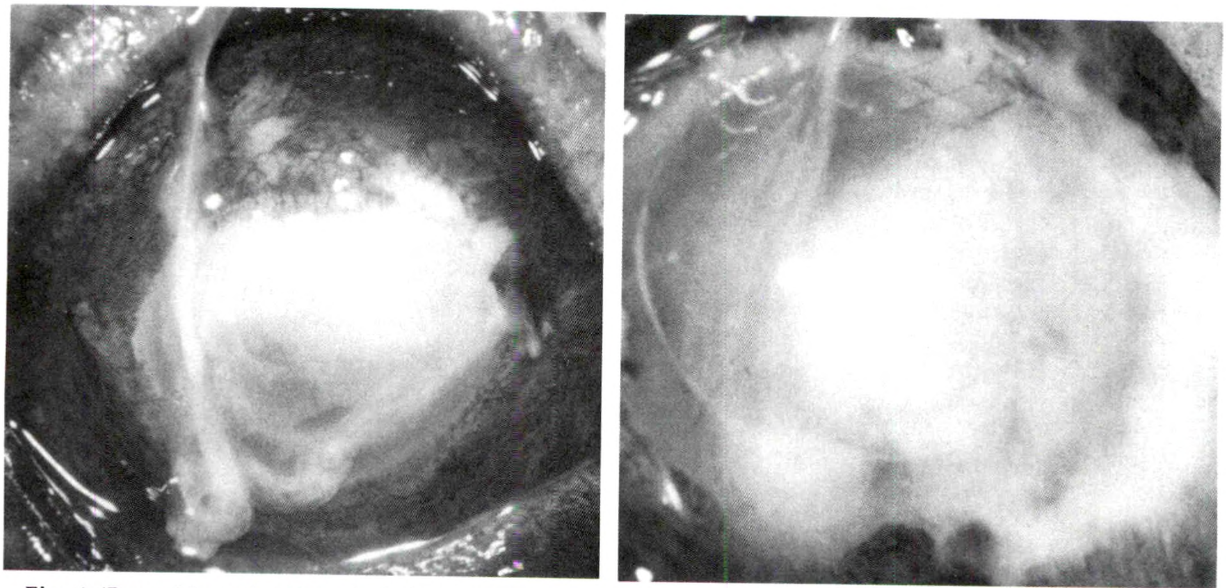

Fig. 1 (Reynolds and Alfonso). Left, Patient with keratoscleritis three weeks after suture removal from a cataract wound. Right, Patient with keratoscleritis one month after graft wound dehiscence and resuturing.

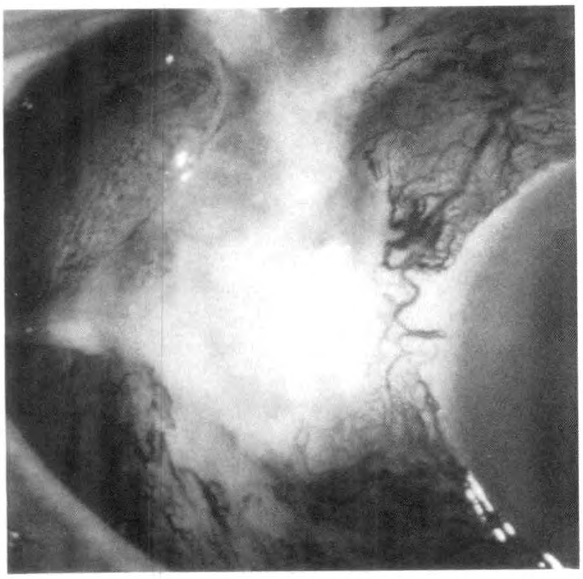

Fig. 2 (Reynolds and Alfonso). Patient with isolated infectious scleritis ten years after pterygium removal and subsequent beta irradiation.

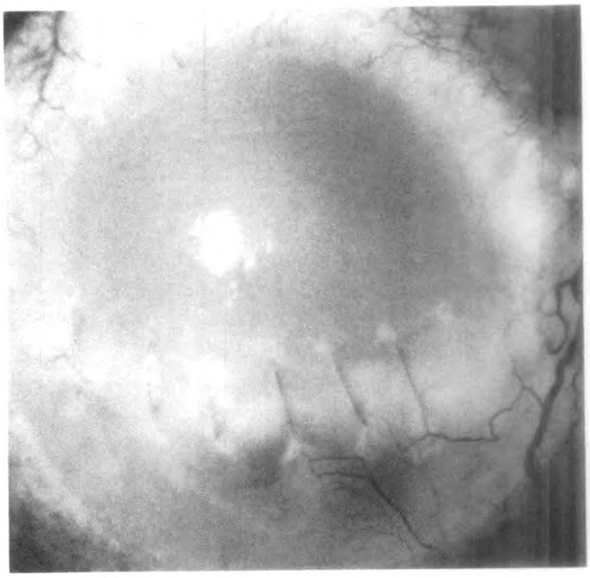

Fig. 3 (Reynolds and Alfonso). Patient at five months after corneoscleral graft for keratoscleritis. Same patient as in Figure 1 (left).

sensitive to amikacin. The patient with keratoscleritis secondary to *Streptococcus pneumoniae* was initially treated with topical cefazolin to which the organism was sensitive, but the treatment was changed to erythromycin because the organism was more sensitive to erythromycin. The patient with keratoscleritis caused by the fungus *Acremonium* was treated with 5% natamycin eyedrops.

Eight patients with keratoscleritis were treated with antibiotics alone. One was treated with eyedrops only, three patients were treated with antibiotic eyedrops and intravenous antibiotics, and four were treated with antibiotic eyedrops and intravenous and subconjunctival antibiotics.

Eleven eyes with keratoscleritis were operated on in addition to being treated aggressively with antibiotics. Conjunctival resection and cryotherapy were performed on four of these eyes. A penetrating corneoscleral graft (9 mm) of the involved tissue was performed on one eye in addition to cryotherapy. Corneoscleral graft (9 and 10 mm) of the involved tissue was performed on two eyes (Fig. 3). Also, large-diameter penetrating keratoplasties (12 and 11 mm) were performed on two eyes, and lamellar corneoscleral patch grafts (12 and 8.5 mm) were performed on two eyes.

Of the nine eyes with isolated scleritis without corneal involvement, five were treated with conjunctival resection and cryotherapy in addition to intensive antibiotics, and the remaining four were treated with aggressive antibiotics alone.

Nine patients with keratoscleritis were treated with corticosteroid eyedrops. In most cases, corticosteroid treatment was not begun until after at least three days of intensive treatment with antibiotics; however, in two cases, treatment with corticosteroid eyedrops was begun immediately, but one of these patients had also received a lamellar corneoscleral graft on the initial day, and treatment with prednisolone acetate eyedrops was begun postoperatively. The other eye in which treatment was begun immediately was eventually enucleated, but none of the other eight eyes in which corticosteroid eyedrops were used was enucleated or eviscerated. Corticosteroid eyedrops were used in eight of the nine patients with isolated scleritis but treatment was not begun until after several days of treatment with antibiotics.

Nine eyes of 19 patients with keratoscleritis were either enucleated or eviscerated, yet none of the isolated cases of scleritis without corneal involvement was lost. Specifically, two eyes of the 11 patients with keratoscleritis that received surgical management were enucleated. One of these patients received cryotherapy, and the other patient received a large-diameter (12 mm) penetrating keratoplasty. Both patients had an initial examination consistent with endophthalmitis. The visual acuities of the nine eyes that had resolution of the infection were the following: hand motions, four; 20/300, two; 20/100, one; 20/70, one; and 20/25, one. The follow-up for these patients ranged from two weeks to 85 months with a mean follow-up of 30 months.

Seven of eight of the eyes treated with antibiotics alone were lost. The one eye that was saved was treated with antibiotic eyedrops, and subconjunctival and intravenous antibiotics and the final visual acuity was 20/50 after 32 months of follow-up after a corneal graft was performed for visual rehabilitation. One patient's eye that was enucleated had progressed to endophthalmitis at initial examination. The average degree of corneal involvement in the 11 eyes treated with surgical management in addition to antibiotics was 30% with a range of 12.5% to 50%, and the average number of clock hours of sclera involved with infection was 3.7 clock hours with a range of two to 12 clock hours. In the eight patients treated with antibiotics alone, the average degree of corneal involvement was 67% with a range of 25% to 100%, and the average number of clock hours of scleral involvement was 5.6 clock hours with a range of one to 12 clock hours. Four patients in this group had completely (100%) infiltrated corneas and all four eyes were enucleated or eviscerated. Removing these four patients from this group, the average degree of corneal involvement in the remaining four patients was 34% with a range of 25% to 50%, and the average scleral involvement was 2.3 clock hours with a range of two to three clock hours.

Discussion

The management of infectious scleritis and keratoscleritis is difficult. Part of the reason for the poor outcome is believed to be poor penetration of antibiotics into the nearly avascular sclera, and possibly the ability of microbial organisms to persist in the avascular intrascleral lamellae for long periods of time without inciting an inflammatory response. As demonstrated in this study as well as in other previous reports, once an infectious keratitis spreads into the adjacent sclera, medical management alone is usually not effective.[1]

In 1981, Raber and associates[1] reported four eyes with keratoscleritis caused by *Pseudomonas* organisms that were treated with intensive antibiotics, all of which required eventual evisceration or enucleation of the eye. Codere, Brownstein, and Jackson[2] described two patients with keratoscleritis caused by *Pseudomonas* organisms who were treated with intensive antibiotics and acetylcysteine eyedrops, one of whom required enucleation of the eye. In 1986, Alfonso and associates[3] reported three cases of keratoscleritis caused by *Pseudomonas* organisms. Patients were treated with intensive antibiotics alone, which resulted in control of the infection in two of the eyes, one of the eyes requiring evisceration, and one of the eyes being left with no light perception. Eiferman[4] reported the benefits of cryotherapy in 1979 when he reported three cases of keratoscleritis caused by *Pseudomonas* organisms that were treated with penetrating keratoplasty and cryotherapy to the remaining cornea and sclera, all of which showed dramatic improvement. Review of the aforementioned literature discloses that approximately 60% of eyes from reported cases with infectious keratoscleritis have undergone evisceration or enucleation or have been left with no light perception.

Various management options have been considered for infectious scleritis and keratoscleritis. Subpalpebral irrigation with antibiotics has been described[6] and transscleral iontophoresis[7] has experimentally shown that high intravitreal amounts of antibiotics can be obtained via scleral penetration by the antibiotics. Also, the CO_2 laser may be of use in scleral infections.[8] These may provide additional options in the management of infectious scleritis, but they have not had common clinical use.

The use of corticosteroid eyedrops in infectious scleritis is controversial. Some believe they should have no role in the treatment of infectious scleritis,[8] whereas others believe they should only be used after several days of intensive antibiotic treatment if the infection is coming under control. However, prolonged use of corticosteroid eyedrops may lead to late recurrence of infection.[9] We recommend the use of corticosteroid eyedrops after an organism has been identified and appropriate antibiotic treatment has been established. Careful clinical monitoring is essential. Corticosteroids help modulate the inflammatory response which in itself may be destructive to the ocular tissues. In some of our cases, scleral inflammation has recurred months after resolution of the initial condition, has been found to be culture negative, and has responded to corticosteroid eyedrops.

The role of cryotherapy in the treatment of infectious scleritis is poorly defined. Studies have shown the effectiveness of cryotherapy in keratitis caused by *Pseudomonas* organisms in rabbits and guinea pigs,[10] but no controlled studies have been performed to show the benefits of cryotherapy in infectious scleritis. Anecdotal reports have shown that it appears to be effective, and this study suggests that it is more effective than the use of antibiotics alone. Possible mechanisms for the efficacy of cryotherapy include mechanical destruction of microorganisms by intracellular and extracellular ice, severe osmotic disequilibration, disruption of DNA, and a host of other enzymatic and cellular alterations.[4,10] It is also possible that cryotherapy enhances the effectiveness of antibiotics by enhancing the penetration through bacterial cell walls or into the sclera.[4,10]

Nine eyes of the 28 patients in this study eventually required enucleation or evisceration. All nine of the lost eyes were cases of keratoscleritis. *Pseudomonas aeruginosa* was responsible for 16 of 19 of the cases of keratoscleritis and for only four of the nine cases of isolated scleritis without corneal involvement. The poorer outcome in patients with infectious keratoscleritis may relate to the greater proportion of virulent organisms in this group.

The prognosis in patients with infectious keratoscleritis is poor with enucleation or evisceration being required in nine of 19 patients in this study to control the infection. Isolated infectious scleritis without corneal involvement appears to have a better prognosis. The outcome of patients with keratoscleritis treated surgically as well as intensively with antibiotics appears better than that of patients treated with antibiotics alone. Undoubtedly, the fact that the patients with keratoscleritis treated medically alone had a greater percentage of the cornea involved (67% compared to 30%) contributed to the discrepancy in outcome. However, when subtracting the four patients who had 100% of their cornea involved from this group, the percentage of corneal involvement was 34% compared to 30% for the group treated surgically. However, three of four of these patients in the medically treated group required enucleation or evisceration of the eye compared to two of 11 for the group treated surgically. The degree of scleral involvement between the two groups was similar.

Although the early management of patients with infectious scleritis or keratoscleritis should continue to include intensive antibiotic eyedrops, subconjunctival, and possibly parenteral antibiotics, strong consideration should be given to surgical management if the patient is not improving within the first few days of antibiotic treatment. Surgical intervention may consist of conjunctival resection with cryotherapy to the immediate surrounding sclera or lamellar or full-thickness procedure to excise the involved cornea and sclera with subsequent graft, or both. The use of corticosteroid eyedrops remains controversial, but this study suggests that although it is not indicated in the initial management, it may be beneficial after several days of intensive antibiotics.

References

1. Raber, I. M., Laibson, P. R., Kurz, G. H., and Bernardino, V. B.: *Pseudomonas* corneoscleral ulcers. Am. J. Ophthalmol. 92:353, 1981.
2. Codere, F., Brownstein, S., and Jackson, W. B.: *Pseudomonas aeruginosa* scleritis. Am. J. Ophthalmol. 91:706, 1981.
3. Alfonso, E., Kenyon, K. R., Ormerod, L. D., Stevens, R., Wagoner, M. D., and Albert, D. M.: *Pseudomonas* corneoscleritis. Am. J. Ophthalmol. 103:90, 1987.
4. Eiferman, R. A.: Cryotherapy of *Pseudomonas* keratitis and scleritis. Arch. Ophthalmol. 97:1637, 1979.
5. Liesegang, T. J., and Forster, R. K.: Spectrum of microbial keratitis in South Florida. Am. J. Ophthalmol. 90:38, 1980.
6. Hessburg, P. C.: *Pseudomonas* corneoscleral ulcers (correspondence). Am. J. Ophthalmol. 93:256, 1982.
7. Barza, M., Peckman, C., and Baum, J.: Transscleral iontophoresis of cefazolin, ticarcillin, and gentamicin in the rabbit. Ophthalmology 93:133, 1986.
8. Tabbara, K. F., and Hyndiuk, R. A.: Infections of the Eye. Boston, Little, Brown and Company, 1986, pp. 477–486.
9. Harbin, T.: Recurrence of a corneal *Pseudomonas* infection. Am. J. Ophthalmol. 58:670, 1964.
10. Alpren, T. V. P., Hyndiuk, R. A., Davis, S. D., and Sarff, L. D.: Cryotherapy for experimental *Pseudomonas* keratitis. Arch. Ophthalmol. 97:711, 1979.

Cold-induced Corneal Edema in Patients With Trigeminal Nerve Dysfunction

Keith H. Baratz, M.D., Stefan D. Trocme, M.D., and William M. Bourne, M.D.

Two previous cases of cold-induced corneal edema have been reported in patients with corneal anesthesia secondary to a trigeminal nerve disorder. We studied six patients with complete unilateral corneal anesthesia after trigeminal ablation. Subjects' eyes were exposed to 4 C air from a fan for one hour. We measured corneal thickness, corneal surface temperature, and endothelial permeability to fluorescein. During cold exposure, two of the six study eyes exhibited reversible corneal swelling (11% and 26% over baseline value). All anesthetic corneas were consistently colder (13.8 ± 0.7 C) than the contralateral corneas (21.0 ± 1.7 C, P = .001). Baseline endothelial permeability and aqueous humor flow rates were similar in both the study and control groups. After cold exposure, the study eyes had a significant transient increase in permeability compared to the controls (7.5 ± 2.4 × 10^{-4} cm/min vs 2.9 ± 1.4 × 10^{-4} cm/min, P = .007). Baseline endothelial photomicrographs also showed increased pleomorphism (fewer hexagonal cells) in the anesthetic corneas. These data suggest that sensory denervation of the eye influences ocular temperature regulation and corneal endothelial cell morphologic characteristics. Some anesthetic corneas are prone to cold-induced edema, which may result from excessive cooling.

TWO RECENT REPORTS describe patients with unilateral cold-induced corneal edema associated with ipsilateral trigeminal neuropathy.[1,2] In both cases, substantial corneal swelling ensued rapidly after exposure to a cold ambient temperature. Edema subsided within several hours after returning to room temperature (20 C). In each patient, only the anesthetic cornea was measurably affected, even though the contralateral eye was subjected to the same environmental conditions. Thorgaard, Holland, and Krachmer[1] measured the corneal surface temperature in their subject with a contact thermocouple. They found both eyes to be the same temperature during cold exposure. The conclusion drawn from these studies was that the denervated cornea was prone to cold-induced edema. A mechanism for such a neural influence is not known.

We examined a group of patients with unilateral trigeminal nerve dysfunction in order to determine whether cold-induced edema is a universal finding in the anesthetic cornea. In an effort to measure endothelial morphologic characteristics and function we have included specular microscopy and fluorophotometry in the examination of these patients. Corneal surface temperature was also monitored, because this variable may influence corneal edema. Studies performed by Mapstone[3] on the temperature and the infrared emission characteristics of the anterior segment indicate the usefulness of noncontact infrared bolometry for corneal temperature measurements.

Subjects and Methods

We selected six patients with complete unilateral trigeminal nerve dysfunction resulting from surgical treatment at least three years previously for cluster headaches. Subjects 1, 2, 3, 5, and 6 underwent selective percutaneous radiofrequency thermocoagulation of the gasserian ganglion affecting the first and second divisions of the trigeminal nerve. Subjects 2

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and 4 underwent complete retrogasserian rhizotomy of the sensory root of the trigeminal nerve via suboccipital craniectomy (Subject 2 underwent both thermocoagulation and rhizotomy on the same side, one month apart). Subject 1 underwent bilateral procedures, and the remaining five subjects underwent unilateral procedures. After informed consent, each patient underwent a thorough ophthalmic examination of visual acuity, pupils, visual fields, extraocular movements, applanation tonometry, slit-lamp biomicroscopy, and ophthalmoscopy. Symmetry of pupil size and interpalpebral fissures was noted in order to exclude the possibility of a concomitant Horner's syndrome. Corneal sensation was tested by Cochet-Bonnet esthesiometry. This measures the cornea's sensory threshold to the tip of a fine 6-cm-long nylon filament extended from a pencil-shaped barrel.[4] As the nylon filament is drawn up into the barrel, the filament becomes stiffer and less easily bent, thereby exerting more pressure at the tip. Tear secretion was measured using conventional filter-paper strips both before (Schirmer I test) and after (basal tear secretion test) instillation of 0.5% proparacaine solution. Baseline corneal thickness was calculated as the mean of three consecutive measurements with a modified optical pachymeter.[5] Each eye had baseline wide-field endothelial photography and slit-lamp photography performed. These were used to determine anterior chamber volume,[6] which is necessary for anterior segment fluorophotometry. The autofluorescence of each cornea and anterior chamber was measured with a two-dimensional scanning ocular fluorophotometer.[7]

Anterior segment fluorophotometry was performed the next day. At 2 A.M. one drop of 2% sodium fluorescein was instilled in each eye. This dose was repeated at five-minute intervals for a total of five drops in the contralateral control eye and two drops in the study eye. Preliminary studies indicated that equivalent doses of fluorescein eyedrops produce higher stromal concentrations in denervated corneas compared to normal corneas. At hourly intervals from 8 A.M. to 11 A.M., a two-dimensional scanning ocular fluorophotometer measured corneal stromal and aqueous humor fluorescence at 488 nm in a manner described by McLaren and Brubaker.[7] After the 11 A.M. measurement, the subjects entered a cold room maintained at 4 C. They were placed 35 to 40 cm in front of a rotary desk-top fan directed at the face. Corneal surface temperature was measured with an infrared bolometer (Linear Laboratories, Model C600-M, Mountain View, California), the probe being held 2 cm from the cornea. Corneal temperature was recorded for each eye at 15-minute intervals during cold exposure. While in the cold room, we also monitored blink frequency and symmetry of eyelid closure. After 60 minutes, the subjects left the cold room. Fluorophotometry, optical pachymetry, bolometry, and slit-lamp examination were then performed every 15 minutes for two hours and then hourly for an additional two to three hours. All values of corneal thickness represent the mean of three consecutive readings with the optical pachymeter.

Corneal endothelial permeability was calculated from the fluorophotometry data using the methods of Jones and Maurice[8]:

$$\text{Permeability} = k_{c.ca}\, q\, r_{ca}$$

where q is the mean stromal thickness, which is estimated to be the total central thickness,[9] and r_{ca} is the fluorescein distribution ratio between the cornea and the anterior chamber, on the basis of the observation that protein binding of fluorescein produces a stroma:aqueous humor ratio of fluorescein greater than unity at steady state.[8]

$$\text{The transfer coefficient } k_{c.ca} = \frac{\Delta C_c}{(r_{ca}\bar{C}_a - \bar{C}_c)\,\Delta t}$$

where $\bar{C}_c$ = average corneal concentration of fluorescein over the time interval Δt, and $\bar{C}_a$ = average anterior chamber concentration of fluorescein over the interval Δt, and ΔC_c = the change in corneal fluorescein concentration over the interval Δt. The average fluorescein concentrations were determined from concentrations measured at the beginning and end of each time interval:

$$\bar{C} = \frac{C_1 - C_2}{\ln\,[C_1/C_2]}$$

We made two additional adjustments in our calculations of endothelial permeability in order to attempt to correct for the uncertainties introduced when corneal thickness changes over the measurement interval. First, the effect of active corneal swelling or thinning upon the fluorescein distribution ratio (r_{ca}) was estimated. As the cornea swells, the stromal protein concentration will decrease, assuming soluble proteins do not transfer into or out of the cornea. From the law of mass action,[10] the adjusted distribution ratio is:

$$r_{ca} = \left(\frac{q_o}{r'_{ca}\,q_t} - \frac{q_o}{q_t} + 1\right)^{-1}$$

where r'_{ca} is the steady-state distribution ratio for fluorescein in human corneas of normal thickness, and q_o and q_t represent the corneal thickness at the beginning and end, respectively, of the time interval measured. We used 1.6 as the value for r'_{ca}.[11]

The second correction that we made to allow for the effects of changing corneal thickness was the estimate of stromal fluorescein concentration. In our fluorophotometry system, the size of the focal diamond on the cornea, which is formed by the intersection of the exciting laser beam and the optical pathway into the photomultiplier tube, is thicker than the cornea itself. Therefore, the fluorescence obtained from the focal diamond reflects corneal fluorescein as well as the adjacent air, tear film, and aqueous humor. As the cornea swells, the efficiency of the focal diamond increases, because a greater proportion of the diamond is included within the cornea. Given a mild to moderate degree of corneal swelling, we may assume in our system that the relationship between the efficiency of the focal diamond, $e_{f.d}$, and the changing corneal thickness is linear:

$$e_{f.d} = mq + b$$

For our equipment, $m = 0.86\ mm^{-1}$ and $b = 0.29$.

The true corneal fluorescein concentration, C_c, was determined on the basis of the focal diamond efficiency at the corneal thickness at which the fluorescence measurement was made:

$$C_c = \frac{C'_c}{e_{f.d}} \text{ or } C_c = \frac{C'_c}{mq + b}$$

where C'_c is the uncorrected measurement of corneal fluorescein concentration.

Specular photomicrographs of the central corneal endothelium of each eye were projected at a magnification of × 500. The vertices of 100 adjacent cells for each cornea were marked and then digitized to find cell area and the number of sides per cell. Polygonality and the coefficient of variation of cell area (standard deviation divided by mean) were determined from these data.

All data were analyzed using the two-tailed Student *t*-test for paired samples. A probability of .05 or less was considered statistically significant.

Results

Corneal esthesiometry—Complete unilateral corneal anesthesia was confirmed by Cochet-Bonnet esthesiometry in all six patients (a reading of 0 on a scale of 0 to 6.0, with 0 being complete anesthesia). Subject 1, who had been treated for bilateral cluster headaches, had complete anesthesia on one side but near-normal skin and corneal sensation on the other side. The central corneal sensation on the latter side was measured as 4.0. The control eyes in the other five subjects had a mean central corneal sensation of 5.9 (range, 5.5 to 6.0). Because the one cornea in Subject 1 had only mildly decreased sensation, it was included with the control group of fellow eyes.

Corneal thickness—As a result of cold exposure, two of the six anesthetic corneas swelled (Table 1). Before cold exposure, baseline corneal thicknesses in these eyes were similar to their fellow controls. None of the control eyes nor any of the other four study eyes exhibited corneal edema. Remarkable swelling was defined as a 5% increase in thickness over baseline value. The corneal thickness of the study eye increased 11% (0.540 to 0.608 mm) in Subject 1 and 26% (0.515 to 0.647 mm) in Subject 2. In both cases, swelling was evident at the first postcold pachymetric measurement, 15 minutes after leaving the cold room. At this time, thicknesses were 0.573 mm and 0.627 mm, but the maximal thickness was not attained until 90 minutes and 45 minutes after leaving the cold room in Subjects 1 and 2, respectively. In both subjects, the visual acuity in the affected eye had decreased from 20/20 to 20/40, whereas the control eye had remained at 20/20. Slit-lamp examination of these corneas exhibited stromal haze and Descemet's folds. The findings were more pronounced in Subject 2, whose cornea also had epithelial bedewing. Both corneas gradually returned to their baseline thicknesses within two hours.

Temperature—At room temperature, the denervated eyes had a corneal surface temperature similar to the contralateral control eyes

TABLE 1

RESULTS OF PACHYMETRY AND FLUOROPHOTOMETRY AFTER COLD EXPOSURE IN STUDY EYES AND CONTROL EYES

		CORNEAL THICKNESS (MM)		ENDOTHELIAL PERMEABILITY (× 10^{-4} CM/MIN)					
EYES	MEAN TEMPERATURE IN COLD (C)*	BASELINE VALUE	MAXIMUM VALUE AFTER COLD EXPOSURE	BASELINE VALUE	VALUE AT COLD EXPOSURE†	VALUE 15 TO 45 MINUTES AFTER COLD EXPOSURE	VALUE 50 TO 267 MINUTES AFTER COLD EXPOSURE	BASELINE AQUEOUS HUMOR FLOW RATE (μL/MIN)	BASELINE INTRAOCULAR PRESSURE (MM HG)
Corneal Thickness and Permeability of Study Eyes									
Subject 1	14.9	0.540	0.608	5.19	1.08	6.93	3.87	3.60	12
Subject 2	13.8	0.515	0.647	2.97	4.04	11.58	4.25	1.80	12
Subject 3	13.5	0.510	0.528	4.22	1.37	5.51	3.75	2.20	15
Subject 4	14.4	0.560	0.575	5.69	2.16	6.97	4.41	4.42	18
Subject 5	13.6	0.598	0.602	4.12	2.85	6.54	4.35	1.87	12
Subject 6	12.9	0.603	0.633	—	—	—	—	—	15
Mean	13.8	0.554	0.600	4.44	2.30	7.51	4.13	2.78	14.0
(± SD)	(0.7)	(0.040)	(0.043)	(1.05)	(1.19)	(2.35)	(0.30)	(1.17)	(2.45)
Corneal Thickness and Permeability of Control Eyes									
Subject 1	20.2	0.548	0.573	4.38	4.40	1.62	3.56	3.35	13
Subject 2	24.0	0.517	0.515	5.00	5.50	4.08	4.65	3.16	13
Subject 3	20.8	0.522	0.530	4.12	2.40	1.84	3.65	2.34	13
Subject 4	21.1	0.565	0.568	5.91	4.10	4.63	4.92	4.00	17
Subject 5	18.7	0.595	0.600	3.19	2.72	2.34	5.08	1.58	12
Subject 6	21.5	0.617	0.627	—	—	—	—	—	15
Mean	21.0	0.561	0.569	4.52	3.82	2.90	4.37	2.89	13.8
(± SD)	(1.7)	(0.040)	(0.042)	(1.01)	(1.27)	(1.37)	(0.72)	(0.94)	(1.83)
P value‡	.001	.057	.213	.879	.054	.007	.275	.753	.738

*Mean temperature in each eye was determined as the mean of the bolometer measurements after 30, 45, and 60 minutes of cold exposure.

†The 90-minute interval was from 15 minutes before entering the cold room to 15 minutes after leaving the cold room.

‡Two-sided Student *t*-test for paired samples.

(34.3 C vs 34.9 C). Upon cold exposure, all eyes became colder. The study group of eyes became markedly colder than their fellow eyes, however (Table 1). The mean temperature of the study corneas, as found by calculating the mean of the temperature readings after 30, 45, and 60 minutes of cold exposure, was 13.8 ± 0.7 C compared to 21.0 ± 1.7 C for the controls (P = .001). The mean temperature for the two study corneas that swelled was 14.9 and 13.8 C compared to 13.6 C for those study corneas that displayed no marked change in thickness. The eyelid fissure width and blinking were similar between both eyes of all subjects. The temperature difference between the normal and anesthetic sides was not confined to the globes. The entire skin surface region supplied by the involved portions of the trigeminal nerve was colder on the denervated side. After removal from the cold, both eyes in all subjects returned to normal precold temperatures. This occurred by the time of the first postcold measurement, approximately 15 minutes after leaving the cold room.

Endothelial permeability—Fluorophotometry data were examined for five of the six subjects who underwent cold exposure (Table 1, Fig. 1). Data from Subject 6 were excluded from this portion of the study because the fluorescein concentration in the anesthetic cornea was extremely high (> 3,000 ng/ml). We considered our equipment to be inaccurate at such high concentrations.

Baseline permeability values before cold exposure were similar in the study and control groups (4.44 ± 1.05 vs 4.52 ± 1.01 × 10^{-4} cm/min). During cold exposure, both groups exhibited a decrease in permeability that was

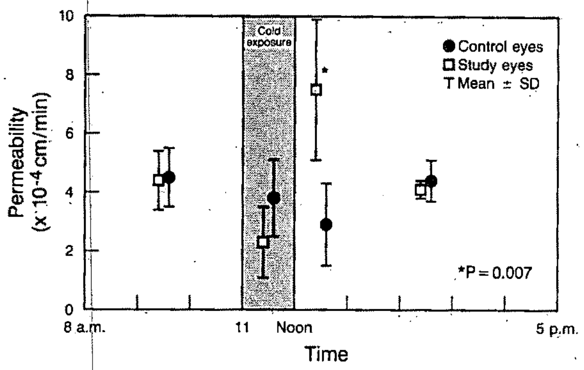

Fig. 1 (Baratz, Trocme, and Bourne). Corneal endothelial permeability to fluorescein before, during, and after cold exposure in five subjects.

more profound in the anesthetic eyes. The difference between the two groups, however, was only of borderline significance (2.30 ± 1.19 vs 3.82 ± 1.27 × 10^{-4} cm/min; $P = .054$). After cold exposure, there was a dramatic, transient increase in permeability in the study group. A similar effect was not evident in the control group. During the 30 minutes after the first postcold-exposure measurement (15 to 45 minutes postcold exposure), the endothelial permeability of the anesthetic eyes differed significantly from the controls (7.51 ± 2.35 vs 2.90 ± 1.37 × 10^{-4} cm/min; $P = .007$). From 50 to 267 minutes after cold exposure, the permeabilities were again similar.

Intraocular pressure and aqueous humor flow—The baseline intraocular pressure was normal in all subjects (Table 1). Aqueous humor production was measured fluorophotometrically during the 8 A.M. to 11 A.M. baseline recordings. There was no statistically significant difference between the study group and control group of eyes (2.78 ± 1.17 vs 2.89 ± 0.94 μl/min).

Endothelial morphologic characteristics—Endothelial characteristics between the study eyes and their contralateral controls were significantly different (Fig. 2). Pleomorphism, measured as an inverse function of the mean percentage of hexagonal cells, was significantly greater in the anesthetic eyes (Table 2). The study eyes averaged 56% ± 5% hexagonal endothelial cells compared to 66% ± 6% in the controls ($P = .009$); the mean and coefficient of variation of cell area were similar in the anesthetic and control groups (Table 2).

Tear production—Tear production measured by filter-paper strips before and after anesthesia was achieved with anesthetic eyedrops was normal and similar in both eyes of all subjects. Eyelid closure was also similar in both eyes, and lagophthalmos was not observed.

Discussion

We included the second eye of Subject 1 in the control group even though it had mildly decreased sensation. We thought that this was justified because its functional measurements were similar to those of the control group and clearly different from its mate (Table 1). Conversely, the morphologic measurements in the second eye of Subject 1 resembled those of the denervated eyes (polymegethism and pleomorphism) more than those of the control group (Table 2). In any case, if both eyes of Subject 1 are omitted from the study, the statistically significant differences are still present (mean temperature in cold, $P = .002$, $N = 5$; endothelial permeability 15 to 45 minutes after cold exposure, $P = .025$, $N = 4$; and percent of hexagonal cells, $P = .009$, $N = 5$).

Edema of the cornea subjected to cold in vitro has been extensively studied.[12-15] Reversibility of swelling when the cornea returns to physiologic temperature has also been clearly demonstrated. In vivo studies have been performed in rabbits in which flow-through contact lenses perfused with cold saline solution–induced corneal edema.[16] In humans, cold-induced corneal changes unrelated to trigeminal neuropathy have only been described in severe environmental conditions.[17,18]

Cooling of the in vitro cornea results in a decreased electric potential across the endothelial surface.[15,19] Additionally, the reversibility of swelling is oxygen-dependent and inhibited by antimetabolites, implicating the energy-dependent endothelial pump as the temperature-sensitive mechanism.

Bito, Roberts, and Saraf[20] examined the cornea's response to cold in hibernating woodchucks.[20] Comparable to experiments in other mammals, the cornea in vitro became edematous at temperatures of 5 C and 11 C. Interestingly, the in vivo corneas of hibernating woodchucks thickened only 7% at temperatures less than 10 C. The reason for the in vivo cornea's resistance to cold-induced edema is not known. Nor is it known whether intact neural pathways to the cornea are instrumental in preventing edema in such circumstances.

In our study, one third of the denervated corneas swelled markedly (defined as a 5%

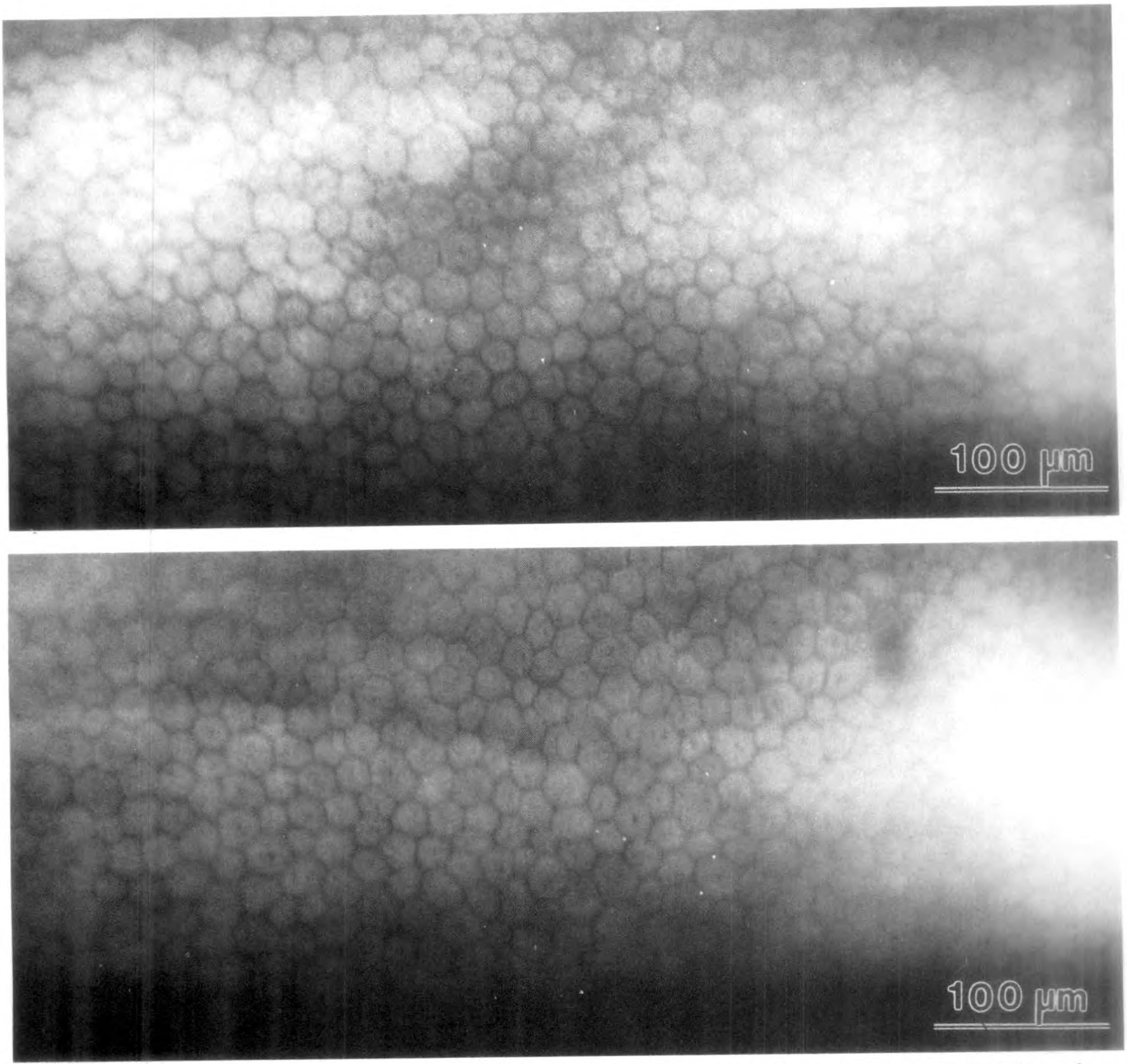

Fig. 2 (Baratz, Trocme, and Bourne). Wide-field specular photomicrographs of corneal endothelium from anesthetic eye (top) and normal eye (bottom) from Subject 2 at normal ambient temperature, demonstrating polymegethism and pleomorphism in the anesthetic eye.

increase over baseline thickness) during cold exposure, whereas none of the normal eyes did. A confounding variable was evident that made data interpretation more difficult; all anesthetic eyes became considerably colder than the contralateral control eyes. Therefore, a tendency for corneas to swell upon cold exposure cannot be solely attributed to the denervated state but may also be a function of how cold the tissue becomes. The corneas that swelled, however, were not colder than the denervated corneas that did not swell. We cannot determine from this study whether the decreased temperature in the denervated corneas is sufficient to account for the observed swelling, or whether other factors are involved. This temperature difference is in contrast to the findings described by Thorgaard, Holland, and Krachmer.[1] Wilson, Garrity, and Bourne[2] did not report corneal temperatures during cold exposure.

Previous reports of cold-related corneal disease in normal eyes described individuals exposed to extreme conditions.[17,18] In these early cases, the corneal findings included epithelial defects and stromal haze, but corneal thicknesses were not reported. It is unclear whether

TABLE 2
CORNEAL ENDOTHELIAL MORPHOLOGIC CHARACTERISTICS IN STUDY EYES AND CONTROL EYES

EYES	MEAN CELL AREA (μM^2)	COEFFICIENT OF VARIATION OF CELL AREA	HEXAGONAL CELLS (%)
		Study Eyes	
Subject 1	373	0.31	54
Subject 2	410	0.31	52
Subject 3	393	0.40	60
Subject 4	398	0.41	50
Subject 5	371	0.30	58
Subject 6	285	0.23	61
Mean	372	0.33	56
(± SD)	(45)	(0.07)	(5)
		Control Eyes	
Subject 1	347	0.34	57
Subject 2	373	0.24	71
Subject 3	455	0.28	72
Subject 4	369	0.29	64
Subject 5	311	0.32	63
Subject 6	359	0.31	70
Mean	369	0.30	66
(± SD)	(47)	(0.04)	(6)
P value*	.905	.570	.009

*Two-sided Student *t*-test for paired samples.

these changes resulted from cold-induced alterations in corneal hydration or from actual freezing of the tissues. It has not been described whether normal in vivo human corneas swell when subjected to less harsh conditions comparable to the 10 to 15 C temperatures attained by our study eyes. One study showed that during a small decrease in temperature (from 35 C to 25 C) no swelling in rabbit corneas in vitro was observed despite a decrease in electric potential across the endothelium.[19] The hypothesis offered was that a passive decrease in endothelial permeability, as evidenced by a decreased electric conductivity, or a temperature-dependent increase in water viscosity was sufficient to offset the diminished ion pump rate.[19,21,22] It is possible that these homeostatic mechanisms allowed the control eyes to maintain a steady corneal thickness over the temperature range at which we studied them. Perhaps the control eyes might not have been able to maintain normal hydration if colder temperatures were attained. These proposed ideas, however, do not negate the possibility of a direct neural influence on corneal thickness.

Interactions between nerves and corneal endothelial cells have not been elucidated. One researcher has been able to identify nerve terminals on the corneal endothelium in rabbits.[23] Some interactions between the epithelium and nerve supply have been established. Alper,[24] after producing trigeminal nerve lesions succeeded by tarsorrhaphy in monkeys, found that the denervated eye produced a thinner corneal epithelial layer with less mitotic activity. Other in vitro and in vivo studies have disclosed that corneal epithelial factors can induce growth and differentiation of neuronal tissue.[25-27] In these studies, similar interactions between neural tissue and endothelium were not found.[25]

In our patients, the endothelium of the study eyes expressed greater pleomorphism compared to the controls. Perhaps this results from a lack of trophic neural factors. Such factors could reach the endothelium via corneal nerves or by dissolution in the aqueous humor of compounds produced in the anterior chamber or by the ciliary body. This idea is merely speculative, as no supporting laboratory evidence exists. An alternative explanation for endothelial pleomorphism may be chronic cold stress, because the denervated eye would be frequently colder than normal in persons living in cold environments.

Fluorophotometry of the anterior segment was used as an adjunct to evaluate endothelial function. The baseline values in the study and control groups were similar. The decrease in fluorescein permeability in the anesthetic group during cold exposure was of borderline significance (P = .054). The small sample size may be contributory. If fluid viscosities and the passive diffusion of solutes are considerably altered by cooling in this tissue, then the colder study eyes might be expected to have less fluorescein movement across the endothelium during this time. Another possibility is the solvent drag effect resulting from net fluid flux across a membrane. If the cornea swells during cold exposure, the movement of water into the cornea from the anterior chamber may interfere with the simple diffusion of fluorescein out of the cornea. This would cause a misleadingly low permeability value during the time of active swelling. If solvent drag were operative, one would expect the lowest measured permeability to be in the cornea that swells the greatest and essentially no change in those corneas that do not become edematous. This was not the case in our study. The cornea that swelled the most had the highest permeability during cold exposure (4.04×10^{-4} cm/hr), whereas the only other cornea that swelled had the lowest permeability (1.08×10^{-4} cm/hr). The study corneas that did not swell still exhibited a decreased permeability compared to their controls.

The immediate postcold period was characterized by a marked increase in fluorescein permeability in the anesthetic eyes. Again, all study eyes showed such a response, including those that did not swell. Study-cornea 2, which swelled the most, did have the highest permeability for the first 30 minutes after returning from the cold room. The corneal thickness remained relatively stable during this time interval, so a solvent drag effect cannot be easily implicated. Fluid viscosity also should not have been a factor, because the tissues returned to normal temperature by the first postcold measurement at the start of the 30-minute interval.

Our study found no difference in baseline aqueous humor flow rates between the denervated and control eyes. In Subject 2, whose cornea also exhibited the greatest cold-induced edema, however, the aqueous flow rate was markedly lower in the anesthetic eye compared to that of the fellow eye (1.80 vs 3.16 μl/min). The patient studied by Wilson, Garrity, and Bourne[2] also had a lower aqueous flow rate in the eye with sensory denervation (2.82 vs 4.33 μl/min). In reviewing fluorophotometry data from 80 healthy subjects previously reported from our institution,[9] we found an asymmetry of aqueous flow rate greater than 0.70 μl/min in only two individuals. Belmonte and associates[28-30] have extensively studied neuronal activity to the eye in relation to intraocular pressure. They found that changes in intraocular pressure caused alterations in the neuronal discharges from afferent ciliary nerves[28] as well as from efferent ciliary nerves.[29] Prolonged stimulation of the cervical sympathetic ganglion also caused a 12% to 19% decrease in aqueous flow rate.[30] Hypothetically, a neural feedback loop involving the afferent activity of the trigeminal nerve could exist as a mechanism for controlling intraocular pressure.

The temperature regulation of the anesthetic cornea proved to be an unexpected variable. The cornea, lacking a direct blood supply, is reliant upon its local environment, including the eyelids, tear film, surface evaporation, aqueous humor, environmental temperature, and regional blood flow for the determination of its temperature. In this study, cold exposure caused a decrease in temperature of the denervated cornea in comparison to the contralateral controls. Mapstone[31] and Rysä[32] theorized that marked asymmetry of corneal temperature was caused by vascular influences. The increased corneal temperatures of eyes with uveitis and decreased temperatures of eyes ipsilateral to carotid stenoses were given as examples. Other determinants of corneal temperature caused less dramatic changes and asymmetries. In our subjects, this temperature asymmetry was not limited to the globe but was observed in the region supplied by the first division of the trigeminalnerve. This regional effect is further evidence that tear surface and aqueous humor dynamics are an unlikely cause for excessive cooling. More likely, the sensory denervation of the eye and skin interrupts any feedback mechanisms by which the efferent system may regulate vasodilation to that portion of the face.[33,34]

References

1. Thorgaard, G. L., Holland, E. J., and Krachmer, J. H.: Corneal edema induced by cold in trigeminal nerve palsy. Am. J. Ophthalmol. 103:641, 1987.
2. Wilson, S. E., Garrity, J. R., and Bourne, W. M.: Edema of the corneal stroma induced by cold in trigeminal neuropathy. Am. J. Ophthalmol. 107:52, 1989.
3. Mapstone, R.: Measurement of corneal temperature. Exp. Eye Res. 7:237, 1968.
4. Cochet, P., and Bonnet, R.: L'esthésie cornéene. Clin. Ophthalmol. 4:3, 1960.
5. Mishima, S., and Hedbys, B. O.: Measurement of corneal thickness with the Haag-Streit pachometer. Arch. Ophthalmol. 80:710, 1968.
6. Johnson, S. B., Coakes, R. L., and Brubaker, R. F.: A simple photogrammetric method of measuring anterior chamber volume. Am. J. Ophthalmol. 85:469, 1978.
7. McLaren, J. W., and Brubaker, R. F.: A two-dimensional scanning ocular fluorophotometer. Invest. Ophthalmol. Vis. Sci. 26:144, 1985.
8. Jones, R. F., and Maurice, D. M.: New methods of measuring the rate of aqueous flow in man with fluorescein. Exp. Eye Res. 5:208, 1966.
9. Carlson, K. H., Bourne, W. M., McLaren, J. W., and Brubaker, R. F.: Variations in human corneal endothelial cell morphology and permeability to fluorescein with age. Exp. Eye Res. 47:27, 1988.
10. Taarnhoj, J., Schlecht, L., McLaren, J. W., and Brubaker, R. F.: Calibration of measurements in vivo of fluorescein in the cornea. Exp. Eye Res. 51:113, 1990.
11. Ota, Y., Mishima, S., and Maurice, D. M.: Endothelial permeability of the living cornea to fluorescein. Invest. Ophthalmol. Vis. Sci. 13:945, 1974.

12. Maurice, D. M.: The location of the fluid pump in the cornea. J. Physiol. 221:43, 1972.

13. Dikstein, S., and Maurice, D. M.: The metabolic basis to the fluid pump in the cornea. J. Physiol. 221:29, 1972.

14. Harris, J. E., and Nordquist, L. T.: The hydration of the cornea. I. The transport of water from the cornea. Am. J. Ophthalmol. 40 (suppl.): 100, 1955.

15. Davson, H.: The hydration of the cornea. Biochem. J. 59:24, 1955.

16. McCarey, B., Jumblatt, M. M., and Maurice, D. M.: Cold swells the rabbit cornea in vivo. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1979, p. 162.

17. Colombo, G. L.: Bilateral changes in the corneae following exposure to cold in an airman. Br. J. Ophthalmol. 5:553, 1921.

18. Carrol, F.: Frost bite of the cornea. Am. J. Ophthalmol. 16:994, 1933.

19. Hodson, S.: The regulation of corneal hydration to maintain high transparency in fluctuating ambient temperatures. Exp. Eye Res. 20:375, 1975.

20. Bito, L. Z., Roberts, J. C., and Saraf, S.: Maintenance of normal corneal thickness in the cold in vivo (hibernation) as opposed to in vitro. J. Physiol. 231:71, 1973.

21. Green, K., and Downs, S. J.: Corneal membrane water permeability as a function of temperature. Invest. Ophthalmol. Vis. Sci. 15:304, 1976.

22. Baum, J. P., Maurice, D. M., and McCarey, B. E.: The active and passive transport of water across the corneal endothelium. Exp. Eye Res. 39:335, 1984.

23. Wolter, J. R.: Innervation of the corneal endothelium of the eye of the rabbit. Arch. Ophthalmol. 58:246, 1957.

24. Alper, M. G.: The anesthetic eye. An investigation of changes in the anterior ocular segment of the monkey caused by interrupting the trigeminal nerve at various levels along its course. Trans. Am. Ophthalmol. Soc. 73:323, 1975.

25. Chan, K. Y., and Haschke, R. H.: Action of atrophic factor(s) from rabbit corneal epithelial culture on dissociated trigeminal neurons. J. Neurosci. 1:1155, 1981.

26. ———: Isolation and culture of corneal culture or corneal cells and their interactions with dissociated trigeminal neurons. Exp. Eye Res. 35:137, 1982.

27. ———: Specificity of a neuronotrophic factor from rabbit corneal epithelial cultures. Exp. Eye Res. 41:687, 1985.

28. Belmonte, C., Simon, J., and Gallego, A.: Effects of intraocular pressure changes on the afferent activity of ciliary nerves. Exp. Eye Res. 12:342, 1971.

29. Gallego, R., and Belmonte, C.: Nervous efferent activity in the ciliary nerves related to intraocular pressure changes. Exp. Eye Res. 19:331, 1974.

30. Belmonte, C., Bartels, S. P., Liu, J. H. K., and Neufeld, A. H.: Effects of stimulation of the ocular sympathetic nerves on IOP and aqueous humor flow. Invest. Ophthalmol. Vis. Sci. 28:1649, 1987.

31. Mapstone, R.: Determinants of corneal temperature. Br. J. Ophthalmol. 52:729, 1968.

32. Rysä, P.: Determinants of the corneal temperature under simulated arctic conditions. Acta Univ. Ouluen. Ophthalmol. Otorhinolaryngol. 3:1, 1979.

33. Gonzalez, G., Onofrio, B. M., and Kerr, F. W. L.: Vasodilator system for the face. J. Neurosurg. 42:696, 1975.

34. Lambert, G. A., Bogduk, N., Goadsby, P. J., Duckworth, J. W., and Lance, J. W.: Decreased carotid arterial resistance in cats in response to trigeminal stimulation. J. Neurosurg. 61:307, 1984.

The Career Impact of Keratoconus on Air Force Aviators

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Keratoconus causes progressive blurring and distortion of vision, which threatens the career of a military aviator. To assess the impact of keratoconus on flying careers, we reviewed the records of all aviators with keratoconus who have been examined at the United States Air Force School of Aerospace Medicine over the past 23 years. Of the 22 aviators observed for more than three years, 18 were still qualified to fly at their most recent examination. The remaining four aviators were permanently removed from flying duties because of visual dysfunction caused by keratoconus. Of the 22 aviators examined, 15 required hard contact lenses for optimal correction of vision. No aircraft accidents or incidents, attributable to visual factors, were documented. We concluded that the majority of aviators with keratoconus are able to continue their flying careers safely with the aid of spectacles or contact lenses.

KERATOCONUS is ectatic corneal dystrophy characterized by noninflammatory, apical thinning and conical protrusion of the cornea. This condition usually manifests in young adults as a bilateral, irregular astigmatism that is slowly progressive over seven to eight years. Because military aviators need excellent vision, the progressive blurring and distortion of vision, photophobia, and glare can threaten a flying career.

Before 1965, aviators in the United States Air Force who developed keratoconus were removed from flying status, thereby ending their flying careers. The aviator's expensive training (up to $8 million for a combat-ready pilot) and operational experience are invaluable. Visual rehabilitation is, therefore, economically and professionally important both to the government and the flyers. An earlier report from the Ophthalmology Branch at the United States Air Force School of Aerospace Medicine (now Armstrong Laboratory) detailed our initial findings in 11 aviators.[1]

From 1965 to 1988, 22 flyers with keratoconus were examined and monitored for an average of eight years. The long-term findings and the career impact of keratoconus on these 22 flyers were examined. The data are important to ophthalmologists treating young individuals who are either considering or are participating in flying.

Subjects and Methods

The Ophthalmology Branch is an aeromedical consultant for the United States Air Force Surgeon General concerning aviators who have been grounded for an aeromedically disqualifying ocular abnormality or disease. We try to return as many aviators as possible to flying status, while assuring safe and operational visual function. The vision and visual functions of United States Air Force pilots, navigators, and other aircrew members are checked annually by local flight surgeons. Most flyers with keratoconus were referred to us by their local flight surgeons for evaluation of decreased visual acuity that was not correctable to 20/20 with spectacles.

A complete history was taken from each aviator, and each had a full ocular examination that included, but was not limited to, the following: near and distant visual acuity; ocular motility; stereopsis; pupillary response; color vision; accommodation; manifest and cycloplegic refractions; biomicroscopic examination of the anterior segment; ophthalmoscopic examination with dilated pupils; and keratometry and keratoscopic photography. When necessary, contact lenses were fitted. Keratoconus was diagnosed on the basis of one or more of the following findings: irregular corneal light reflexes on

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ophthalmoscopy or retinoscopy, or irregular mires on keratometry that were unexplained by any other mechanism.[2] The presence of corneal pigment, vertical striae, thinning, or scarring was documented but was not required for diagnosis.

Although 36 aviators were examined, only 22 were monitored for three years or more. Our results are limited to the 22 aviators. The mean follow-up time was 8.1 years (range, three to 18 years). The average number of examinations was six (range, two to 16). The aviators were examined annually. They were examined more frequently, if progression was rapid, and less frequently when symptoms and clinical signs were stable.

Results

Of the 22 aviators meeting the criteria, 12 were pilots, seven were navigators, and three had other aircrew positions. The mean age at diagnosis was 29 years (range, 19 to 41 years; Fig. 1). The following factors were elicited concerning medical history: atopy, two; eye rubbing, one; previous contact-lens wear, six; blunt trauma (not thought to be the cause of keratoconus), two; family history of keratoconus, none.

Blurring and distortion of vision were the most common initial visual complaints. Although 12 aviators denied symptoms, their visual acuity was not correctable to 20/20. Because their job and career depend on being in excellent health, it is not unusual for some aviators to deny symptoms. Seven flyers complained of decreased vision. Three flyers had frequent spectacle changes, and one complained of fatigue while reading. Two aviators had monocular diplopia. Bilateral keratoconus was diagnosed in 15 of the 22 aviators. Thus, a total of 37 eyes were affected by keratoconus. Objective findings included the following: irregular corneal light reflex, 37 eyes; pigment deposition (Fleischer ring), 31 eyes; vertical striae (Vogt's lines), 26 eyes; corneal thinning, 21 eyes; prominent corneal nerves, six eyes; and stromal haze or scar, five eyes.

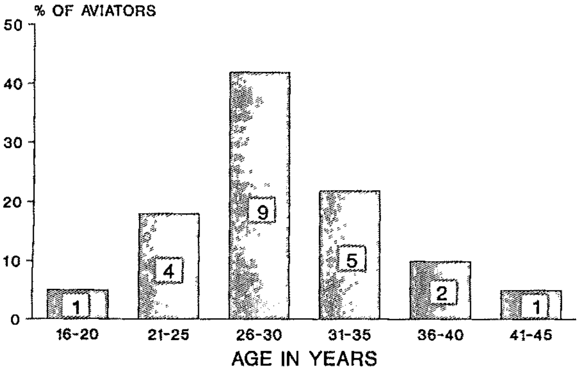

Fig. 1 (Carlson and Green). Age distribution, by percentage of aircrew, at the time of diagnosis. The age range was 19 to 41 years, with a mean age of 29 years.

At the most recent examination, 18 of the 22 aviators were qualified to fly. Only four aviators were permanently disqualified because of visual complications caused by keratoconus. One of these aviators underwent a penetrating keratoplasty, and one underwent thermokeratoplasty. The other two disqualified aviators had poor visual acuity with spectacles and could not tolerate hard contact lenses. They were thought to pose a risk to flying safety.

No aircraft accidents or incidents attributable to visual factors were documented in any of the aviators, either by their report or from the files at the United States Air Force Flight Safety Center.

The four aviators, eventually disqualified from flying because of keratoconus, remained qualified to fly for three, five, eight, and 13 years, respectively (Fig. 2). Eighteen other aviators in whom keratoconus was diagnosed have remained on flying status between three and 18 years. Their flying time, since the diagnosis of keratoconus, averaged 1,183 hours (range, zero to 3,830 hours). Actual flying time depends on job position, because commanders have little or no flying time but are required to remain qualified. The flying time of nonrated crew members is not maintained in the computer files.

Visual function is often difficult to define in keratoconus patients, because the many subjective complaints are difficult to quantify and measurements of Snellen acuity, refractive error, and keratometry reflexes can vary from day to day and between examiners. Nevertheless, for each aviator with at least three examinations, the changes in visual acuity from the time of diagnosis were regressed against time. The change in visual acuity with spectacles over each five years (slope of the line) was designated as that eye's progression per five years. A

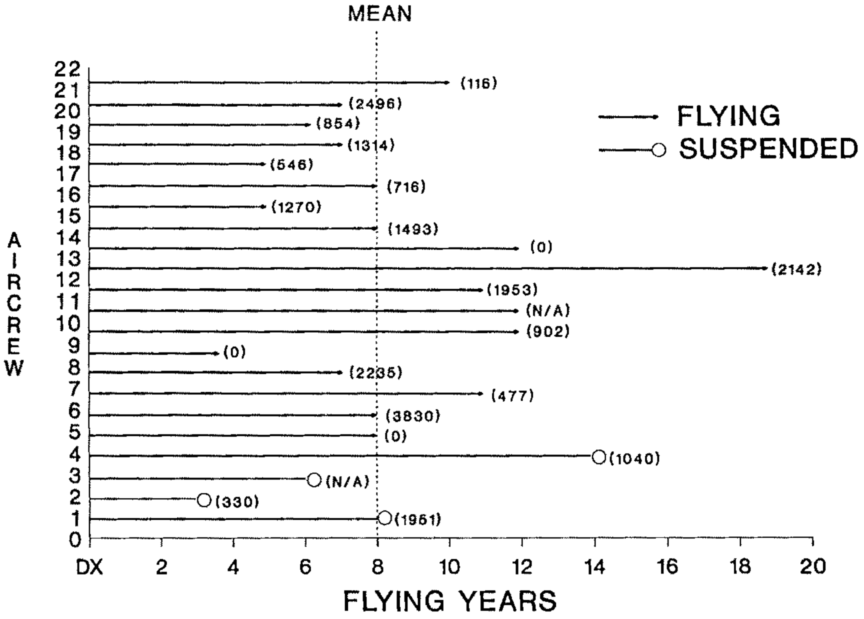

Fig. 2 (Carlson and Green). Individual aircrew flying years after the diagnosis of keratoconus. A career timeline for each aviator is shown. Four individuals were suspended at the times indicated by open circles. The actual flying hours are shown in parentheses. Flying hours for nonrated aircrew are not tabulated and are listed as N/A.

histogram showing the frequency distribution of the progressions per five years was then plotted for the 32 eyes of 19 aviators (Fig. 3). Five eyes of three flyers were excluded, because they did not have a minimum of three data points. In 20 eyes, the best-corrected spectacle visual acuity (recorded in log-scale units) did not change appreciably or actually improved (negative slope). Six eyes lost approximately one Snellen line of visual acuity per five years, and three eyes lost approximately three Snellen lines per five years.

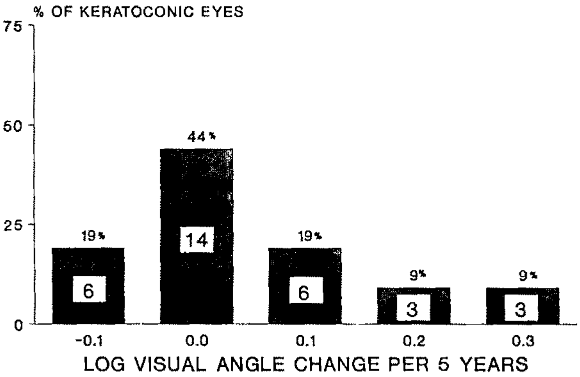

Fig. 3 (Carlson and Green). Rate of visual acuity change with spectacles per five years. A regression line was plotted from diagnosis to last examination. The slope for each eye was designated the progression. The approximate change in the best Snellen visual acuity is listed below the change in log visual angle. Following are the Snellen equivalents: -0.1 = one Snellen line gained: 0.0 = no change; 0.1 = one Snellen line lost; 0.2 = two Snellen lines lost; 0.3 = three Snellen lines lost.

Pilots and navigators are required to have normal stereopsis (25 arc-sec on Vision Test Apparatus). Seven aviators did not meet this standard with spectacles, but all attained normal stereopsis with hard contact lenses.

Initially, 16 of the 37 eyes required hard contact lenses. Eventually, 24 eyes in 15 aviators required hard contact lenses. Hard contact lenses improved visual acuity, stereopsis, and eliminated subjective complaints, such as monocular diplopia (Fig. 4). Nine aviators required bilateral lenses, and six required only one lens.

Despite improvement of visual function, eight of the 15 hard contact-lens wearers admitted to contact-lens problems or complications. Two hard contact-lens wearers had punctated keratitis, one had corneal scanning, two had lens intolerance, one had warped lenses, three were wearing the wrong lens, one had to remove his lens regularly during flight because of ocular fatigue, and one obtained non-Air Force–approved lenses. Some flyers had multiple problems.

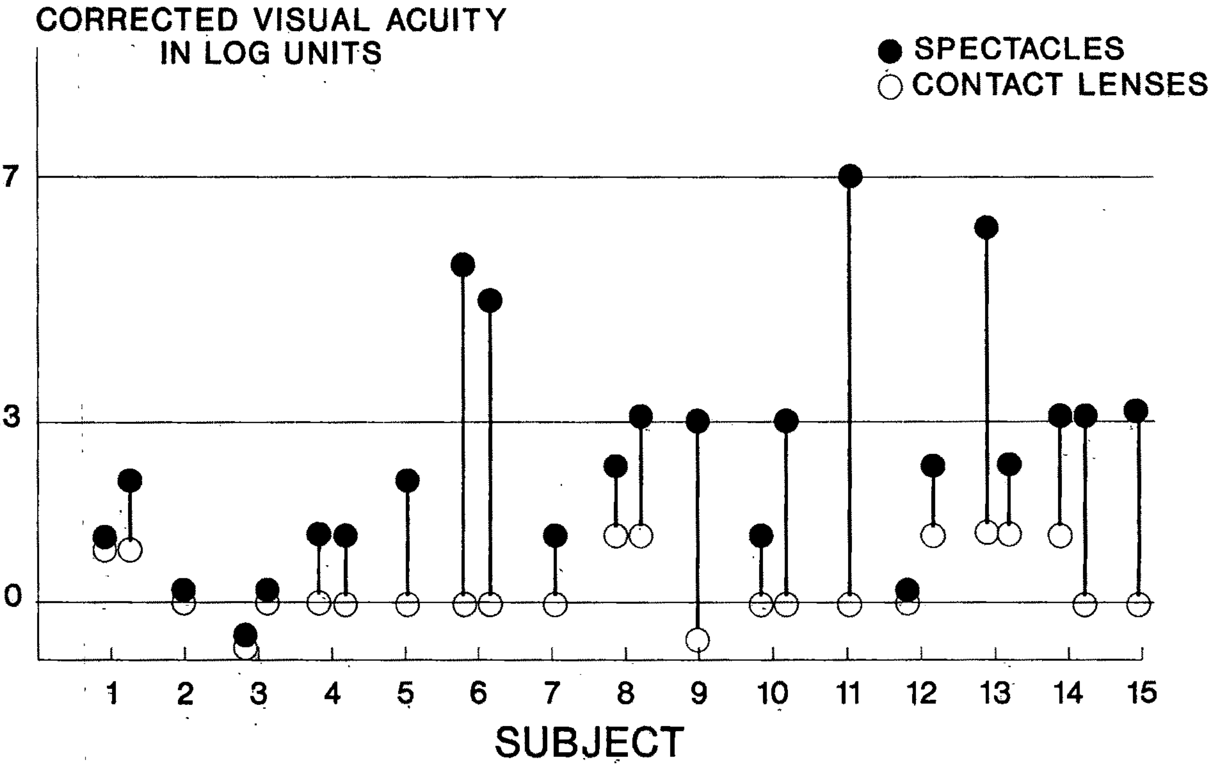

Fig. 4 (Carlson and Green). Best-corrected visual acuities, by subject, spectacle compared to contact lens. The corrected visual acuities are indicated in log units (0 = 20/20; + 0.3 = 20/40; + 0.7 = 20/100). Contact lenses markedly improved vision.

Discussion

This study analyzed the career impact of keratoconus in aviation. We found that 18 of 22 aviators (82%) retained sufficiently good corrected vision, for at least three years, to remain on flying status at their last examination. Rehabilitation using hard contact lenses was crucial and was required in 15 of the 22 aviators (68%). The high rate of admitted contact-lens problems (eight of 15 aviators, 53%) indicates that aviators are not immune to contact lens difficulties.

This patient population is unique in many respects. The group did not include individuals who developed keratoconus early in life before training (ages 22 to 26 years); all of them had visual acuity of 20/20 or better in each eye, many without spectacle correction, when they entered training. Only five of 22 flyers were 25 years or younger at the time of diagnosis. This number contrasts with 20 of 35 individuals in the Mayo Clinic's series.[2] The higher age at diagnosis may indicate a later onset of keratoconus in our group, or a course that was not diagnosed until later in life. Amsler[3] described a slower rate of progression in older patients. Patients with atopy and major blunt trauma are often disqualified from pilot training, and this may explain the low incidence of these associations. The incidence of bilateral keratoconus was similar to that of the Mayo Clinic's experience, but lower than that described by Krachmer, Feder, and Belin.[4] Our group included some individuals with mild, asymptomatic unilateral disease.

Disease progression of two or more lines of lost Snellen visual acuity was comparable to the progression rate reported by Amsler in 1961. This must be carefully interpreted, as many of these aviators were wearing hard contact lenses that can temporarily and artificially cause the cornea to hold a more normal shape. Most of the refractions were done shortly after contact-lens removal.

Military flyers require good vision because of the nature of combat military aviation. They must be fully functional at all times. The visual acuities of trained aviators with keratoconus must be correctable to 20/20 in each eye with contact lenses. Additionally, visual acuity must be at least 20/20 in one eye and no poorer than a full 20/30 in the fellow eye with spectacles. Diplopia should not be evident, even with spectacles. Whether an individual requiring bilateral hard contact lenses should be allowed to continue to fly fighter/attack aircraft is debatable, because of the possibility of contact-lens dislodgement with acceleration, loss of the contact lens from the eye, edge glare, bubbles forming under the contact lenses during rapid decompression, and the like. Hard contact lenses are even less stable on keratoconic eyes because of the abnormal shape. Because of the associated visual, optical, medical, financial, and operational problems, individuals in whom the diagnosis of keratoconus is entertained or in whom keratoconus has been diagnosed should not be entered into any flying training program.

References

1. Barry, W. E., and Tredici, T. J.: Keratoconus in USAF flying personnel. Clin. Aviat. Aerospace Med. 43:1027, 1972.
2. Kennedy, R. H., Bourne, W. M., and Dyer, J. A.: A 48-year clinical and epidemiologic study of keratoconus. Am. J. Ophthalmol. 101:267, 1986.
3. Amsler, M. M.: Quelques donnees du probleme du keratocone. Bull. Soc. Belge Ophtalmol. 129:331, 1961.
4. Krachmer, J. H., Feder, R. S., and Belin, M. W.: Keratoconus and related noninflammatory corneal thinning disorders. Surv. Ophthalmol. 28:293, 1984.

OPHTHALMIC MINIATURE

In Brewer County, but for a few baronial estates ringed by iron fences and moated by miles of lawn, there is nowhere higher to go than these houses; the most successful dentists may get to buy one, the pushiest insurance salesman, the suavest op[h]thalmologists.

John Updike, *Rabbit Redux*
New York, Alfred A. Knopf, 1971, pp. 14 and 15

Anomalous Effect of Subconjunctival Miconazole on *Candida albicans* Keratitis in Rabbits

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After intrastromal injection of a standardized inoculum of *Candida albicans* blastoconidia in Dutch-belted rabbits, the efficacy of subconjunctival therapy with amphotericin B and miconazole was evaluated using a quantitative isolate recovery technique. The subconjunctival injection of miconazole resulted in the recovery of significantly more viable organisms compared to the number recovered in controls (2,000 μg daily, $P < .02$; 3,000 μg daily, $P < .01$, respectively). Amphotericin B, in contrast, in dosages of 500 or 1,500 μg daily, had a significant therapeutic effect ($P < .03$). The anomalous response to subconjunctival therapy with miconazole seen in this model suggests an effect on host defense mechanisms.

SUBCONJUNCTIVAL THERAPY with miconazole has been advocated for the treatment of keratomycosis and intraocular fungal infections, although the efficacy of this form of therapy is still not well-established.[1-4] In the course of investigating antifungal therapy in animal models of keratomycosis, we evaluated the efficacy of miconazole in the treatment of *Candida albicans* keratitis in rabbits. Unexpectedly, isolate recovery rates in the untreated rabbits subjected to miconazole therapy by this route were significantly higher than those in untreated controls and rabbits treated with subconjunctival amphotericin B.

Material and Methods

Animals—Dutch-belted rabbits, 1.5 to 2.5 kg in weight, were used in these studies. Our use of rabbits conformed to the Association for Research in Vision and Ophthalmology resolution on the use of animals in research.

Antifungal agents—Miconazole was obtained as a gift from Janssen Pharmaceutica (Beerse, Belgium) as an intravenous preparation in Cremophor (polyethoxylated castor oil) at a concentration of 10 mg/ml. Different volumes or concentrations of this preparation were used according to the dose required for each experiment. In one experiment this drug solution was diluted with .15 molar saline solution to a concentration of 5 mg/ml.

Amphotericin B was prepared from commercially available Fungizone (Squibb, Princeton, New Jersey). This preparation contains 50 mg of amphotericin B, 41 mg of sodium deoxycholate, and 20.2 mg of sodium phosphate. For intravenous use it is reconstituted in 10 ml of distilled water. This was the formulation used for our series of experiments.

Preparation of inoculum—One-day-old cultures of *C. albicans* (strain VE102) were grown on Sabouraud's dextrose agar. A fresh suspension of the inoculum in sterile .15 molar saline solution was prepared on the day of use such that a 1:10 dilution gave 25% transmission at 550 nm (Bausch & Lomb Model-20 spectrophotometer). The concentration of viable organisms was checked by serial dilution with standard plate counts.

Induction of Candida keratitis—Dutch-belted rabbits were anesthetized with intramuscular ketamine hydrochloride and xylazine hydrochloride. Corneal anesthesia was obtained with instilled 0.5% Ophthaine eyedrops (E. R. Squibb and Sons, Inc., Princeton, New Jersey). Using the operating microscope for visualization, a 30-g disposable needle attached to a 100-μl Hamilton gas-tight syringe was intro-

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duced into the corneal stroma 2 mm from the corneoscleral limbus and advanced to the midstroma of the central cornea. Twenty-five microliters of the inoculum was injected and the needle was removed. If the anterior chamber was penetrated, the rabbit was removed from the study.

Method of subconjunctival injection—Ophthaine 0.5% eyedrops were instilled onto the cornea. The upper eyelid was retracted and a 30-g needle attached to a tuberculin syringe was introduced beneath the conjunctiva nasally to the superior rectus muscle and advanced to a point 5 mm superior to the corneoscleral limbus at the 12 o'clock position. Three hundred microliters of the solution was deposited under the conjunctiva. After removing the needle, the eye was observed for evidence of leakage from the puncture site.

Quantitative isolate recovery—The rabbits were killed with T-61, a commercially prepared euthanasia solution (Taylor Pharmacal, Decatur, Illinois). The whole cornea was removed by excision at the corneoscleral limbus and cut into small pieces. These were then ground with an Ultraturrax Tissumizer Model SDT (Tekmar, Cincinnati, Ohio) in 3 ml of sterile phosphate-buffered saline solution. Aliquots of each corneal suspension (0.1, 1, 10.0, and 100.0 μl) were plated in triplicate and 1,000-μl aliquots in duplicate onto Sabouraud's dextrose agar (BBL, Cockeysville, Maryland). After 48 hours of incubation at 25 C, the colony-forming units were counted and the number of colony-forming units per whole cornea was calculated on the basis of a total volume of 3 ml.[5]

Statistical analysis—The number of colony-forming units recovered from each cornea was expressed as $\log_2$ colony-forming units because the effect of treatment is modeled to be proportional to the pretreatment degree of disease. The effect of a drug treatment was estimated by comparing the mean of the $\log_2$ colony-forming unit measurements of the treated rabbits to the mean of the $\log_2$ colony-forming units of the control rabbits by standard analysis of variance techniques.[6-8]

Experimental Design

Experiment 1—*Candida albicans* infection was established in the right cornea of 18 Dutch-belted rabbits. Twenty-four hours later, treatment was begun with subconjunctival therapy. The rabbits were randomly allocated to three groups. Amphotericin B (300 μl) was administered subconjunctivally, twice daily to the first group of six rabbits (1,500 μg/injection). Miconazole (300 μl) was administered subconjunctivally twice daily to the second group of six rabbits (3,000 μg/injection). The third group of rabbits served as infected, untreated controls. Eighteen hours after the last dose, the rabbits were killed, their infected corneas were removed, and the number of viable fungi in each cornea was determined. This experiment was initially planned to run for five days but was discontinued after three days of treatment because of drug toxicity caused by both agents.

Experiment 2—On the basis of the toxicity observed in the previous experiment, the study was repeated with the drug dosage reduced. The dosage of amphotericin B was reduced to 100 μl once daily (500 μg), and the dosage of miconazole was reduced to 100 μl once daily (1,000 μg). The rabbits were treated for five full days and were killed 24 hours after the last injection. No toxic side effects were observed.

Experiment 3—The same general design was used but 24 rabbits were used in the four randomly allocated groups of Experiment 3. Amphotericin B was administered subconjunctivally to Group 1 as a 100-μl injection once daily (500 μg). Two hundred microliters of a 5-mg/ml preparation of miconazole (1,000 μg) was administered subconjunctivally to Group 2 once daily. Four hundred microliters of the 5-mg/ml preparation of miconazole (2,000 μg) was administered to Group 3 once daily. The fourth group of six rabbits constituted the untreated controls. Treatment was continued for five days; no toxicity was observed. The rabbits were killed and quantitative isolate recovery was performed as in the previous experiments.

Results

The results of the three experiments were analyzed (Table).

Experiment 1—Isolate recovery rates in the miconazole-treated group were significantly higher than those of the controls ($P < .01$). In contrast, isolate recovery rates in the amphotericin B-treated group were significantly lower than those of the controls ($P < .03$).

Experiment 2—In this experiment amphotericin B treatment was efficacious compared to controls ($P < .03$) and miconazole treatment (P

TABLE
QUANTITATIVE ISOLATE RECOVERY AFTER SUBCONJUNCTIVAL THERAPY OF *CANDIDA ALBICANS* KERATITIS IN RABBITS

DRUG	DOSAGE	NO. OF RABBITS	ISOLATE RECOVERY*	P VALUE†
Experiment 1				
Amphotericin B	1,500 μg, twice a day	6	16.26 ± 0.78	<.03
Miconazole	3,000 μg, twice a day	6	19.54 ± 0.14	<.01
Control	—	4‡	18.82 ± 0.13	—
Experiment 2				
Amphotericin B	500 μg, once a day	6	17.66 ± 0.42	<.03
Miconazole	1,000 μg, once a day	6	19.17 ± 0.44	NS§
Control	—	6	18.88 ± 0.16	—
Experiment 3				
Amphotericin B	500 μg, once a day	6	15.85 ± 0.75	=.06
Miconazole	1,000 μg, once a day	6	18.82 ± 0.50	NS
Miconazole	2,000 μg, once a day	6	19.16 ± 0.21	<.02
Control	—	6	17.66 ± 0.46	—

*Mean $\log_2$ colony-forming units ± standard error of the mean.
†As compared to controls.
‡Two control rabbits died.
§Not significant.

< .04). Isolate recovery rates in the subconjunctival miconazole-treated group were not statistically different from those of untreated controls.

Experiment 3—Subconjunctival miconazole in a dosage of 1,000 μg daily had no effect on isolate recovery rates compared to recovery rates of controls. However, when the dose was increased to 2,000 μg, a significantly higher isolate recovery rate was found when compared to recovery rates of untreated controls ($P < .02$). Isolate recovery rates with amphotericin B were marginally lower than they were in controls ($P = .06$) and were significantly lower than the recovery rates of either of the groups treated with miconazole ($P < .01$ and $P < .005$, respectively).

Discussion

The original intent of our study was to evaluate the efficacy of subconjunctival miconazole in the treatment of fungal keratitis in rabbits. The isolate selected to infect the cornea was one that we have used in the past.[5,9,10] By means of topical therapy, we have shown the fungal keratitis to be susceptible to miconazole and amphotericin B in vivo.[3]

The results of miconazole therapy were unexpected. In our laboratory, we have had considerable experience with the use of quantitative isolate recovery with both *Candida* and other fungal infections.[5,9-14] We have found this method to be a useful measure of infection with yeasts, and have used it to study therapy by various routes.

There is some concern, however, regarding the application of quantitative isolate recovery techniques to experimental infections involving fungi.[15] Unlike bacterial infections, in which each viable organism usually represents one potential colony-forming unit, fungal proliferation in the cornea is usually in the hyphal phase. When tissue fragmentation techniques, a necessary prelude to quantitative isolate recovery, are used, the hyphae are presumably broken up into small pieces, some of which then become capable of forming a colony. In this model of keratomycosis, the inoculum is composed largely of *C. albicans* in the blastoconidial phase. As the infection proceeds with tissue invasion, part of the inoculum transforms to the hyphal phase.[16] The application of quantitative techniques captures both phases in the final count. This is important when the effect of a therapeutic agent is being measured. With a fungicidal agent, such as amphotericin B, both blastoconidia and hyphae are likely to be killed as a result of drug action. However, fungistatic agents tend to inhibit hyphal proliferation without necessarily affecting short-term blastoconidial survival.[17] Thus, quantitative isolate recovery may underestimate the effect of a therapeutic modality and, in fact, it is not unusual to be unable to detect the therapeutic effect in such experiments if the period of treatment is relatively short (D.M.O., unpublished data, 1991). However, this type of error caused by insensitivity of the test would be unlikely to extend to overestimating the number of colonies, especially because the technique in other experiments has been shown to provide estimates that are reproducible with relatively low variance.[11,16,18]

We have encountered only two situations in our experience in which a consistent increase in isolate recovery has been noted that could be replicated in successive experiments. Both of these were associated with the use of corticosteroids.[9,19,20] In the first instance, corticosteroid administered subconjunctivally led to a worsening of the infection, not only when the inoculum was *C. albicans*, as in our experiments, but also with *Fusarium* and *Aspergillus* infection.[19,20] The other instance was the abolition of the antifungal action of a marginally effective agent, or an apparent worsening of the disease in the presence of an ineffective antifungal agent, when corticosteroid was administered topically.[9]

In this study we were able to replicate the anomalous effect associated with the subconjunctival injection of miconazole. The contrast with amphotericin B was striking. Moreover, the findings suggest a dose response in that, on the two occasions that it occurred, the amount of miconazole administered was 2,000 μg or greater daily and on the two occasions when it was not detected, the dose administered was 1,000 μg daily. However, we recognize that a formal dose-response experiment was not performed. In another report of subconjunctival miconazole therapy in rabbits with *Candida* keratitis, a clinical improvement was noted with a daily dose of 1,200 mg administered over 21 days.[4]

The penetration of miconazole into the cornea after subconjunctival injection has been studied in rabbits by Foster.[3] The data show that therapeutic levels can be achieved. Although peak levels are high, the transit time through the cornea appears to be brief. A formal comparison of the pharmacokinetics of subconjunctival and topical therapy has not been reported, but studies in our laboratory suggest that topical therapy is more likely to produce sustained concentrations of drug (D.M.O., unpublished data, 1991).

The pharmacokinetics of subconjunctival injection in rabbits differs in some important aspects from subconjunctival injection in humans.[21] Considerable systemic levels are more likely to be achieved even with doses considered to exert only a local effect in humans. Thus, some caution is needed in the interpretation of data from experiments in rabbits.

The reason for the apparent adverse effect of subconjunctival therapy with miconazole on *C. albicans* keratitis is obscure. We have been able to replicate this effect twice, and that variance in counts has not previously extended to an overestimation, which suggests that the observation is valid. The most obvious explanation would appear to be an effect on host defense mechanisms. Azole compounds are known to interfere with arachidonic acid metabolism.[3] Miconazole has been reported to be an inhibitor of thromboxane synthesis but other aspects have not been well-studied.[22] Elucidation of this finding must await further experiments designed to investigate factors affecting interaction of *C. albicans* with the host, but a promising avenue of research would appear to involve arachidonic acid metabolism and its role in the host response.

References

1. Forster, R. K.: The cornea. In Smolin, G., and Thoft, R. A. (eds.): Scientific Foundations and Clinical Practice, ed. 2. Boston, Little, Brown and Company, 1987, pp. 228–240.
2. Koenig, S. B.: Fungal keratitis. In Tabbara, K. F., and Hyndiuk, R. A. (eds.): Infections of the Eye. Boston, Little, Brown and Company, 1986, pp. 331–342.
3. Foster, C. S.: Miconazole therapy for keratomycosis. Am. J. Ophthalmol. 91:622, 1981.
4. Ishibashi, Y., and Kaufman, H. E.: The effect of subconjunctival miconazole in the treatment of experimental *Candida* keratitis in rabbits. Arch. Ophthalmol. 103:1570, 1985.
5. O'Day, D. M., Robinson, R. D., and Head, W. S.: Efficacy of antifungal agents in the cornea. I. A comparative study. Invest. Ophthalmol. Vis. Sci. 24:1098, 1983.
6. Ray, W. A., O'Day, D. M., Head, W. S., and Robinson, R. D.: Statistical analysis for experimental models of ocular disease. Continuous response method. Curr. Eye Res. 4:585, 1985.

7. Ray, W. A., and O'Day, D. M.: Statistical analysis of multi-eyes data in ophthalmic research. Invest. Ophthalmol. Vis. Sci. 26:1186, 1986.

8. Snedecor, G. W., and Cochran, W. G.: Statistical Methods. Ames, Iowa, Iowa State University Press, 1980, p. 242.

9. O'Day, D. M., Ray, W. A., Robinson, R. D., and Head, W. S.: Efficacy of antifungal agents in the cornea. II. Influence of corticosteroids. Invest. Ophthalmol. Vis. Sci. 25:331, 1984.

10. O'Day, D. M., Ray, W. A., Head, W. S., and Robinson, R. D.: Influence of the corneal epithelium on the efficacy of topical antifungal agents. Invest. Ophthalmol. Vis. Sci. 25:855, 1984.

11. Ray, W. A., O'Day, D. M., Head, W. S., and Robinson, R. D.: Variability in isolate recovery rates from multiple and single breeds of outbred pigmented rabbits in an experimental model of *Candida* keratitis. Curr. Eye Res. 3:949, 1984.

12. O'Day, D. M., Robinson, R. D., Williams, T. E., Head, W. S., and Ray, W. A.: Successful treatment of experimental *Aspergillus* keratitis with systemic fluconazole. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 381.

13. O'Day, D. M., Ray, W. A., Robinson, R. D., and Head, W. S.: Correlation of in vitro and in vivo susceptibility of *Candida albicans* to amphotericin B and natamycin. Invest. Ophthalmol. Vis. Sci. 28:596, 1987.

14. O'Day, D. M., Ray, W. A., Robinson, R. D., Head, W. S., and Savage, A. M.: In vitro and in vivo susceptibility of *Candida* keratitis to topical polyenes. Invest. Ophthalmol. Vis. Sci. 28:874, 1987.

15. Rementeria, A., Ezkurra, P., Hernando, F., Ponton, J., Sevilla, M. J., and Cisterna, R.: Chitin assay to estimate the growth of *Candida albicans* in organs of infected mice. J. Med. Vet. Mycol. 29:15, 1991.

16. O'Day, D. M., Ray, W. A., Robinson, R. D., Head, W. S., and Savage, A.: The influence of yeast growth phase in vivo on the efficacy of topical polyenes. Curr. Eye Res. 6:363, 1987.

17. Borgers, M., and Van De Ven, M. A.: Degenerative changes in fungi after itraconazole treatment. Rev. Infect. Dis. 9:533, 1987.

18. O'Day, D. M.: Orally administered antifungal therapy for experimental keratomycosis. Trans. Am. Ophthalmol. Soc. 88:685, 1990.

19. O'Day, D. M., Head, W. S., and Robinson, R. D.: Effect of corticosteroid administration on *Fusarium solani* keratitis in rabbits. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 1169.

20. Head, W. S., O'Day, D. M., Robinson, R. D., and Williams, T. E.: Effect of corticosteroid administration on modeling keratomycoses in the rabbit. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 447.

21. Maurice, D. M., and Mishima, S.: Ocular pharmacokinetics. In Sears, M. L. (ed.): Pharmacology of the Eye. New York, Springer-Verlag, 1984, pp. 67–71.

22. Steinhilber, D., Joschoenek, K., Knospe, J., Morof, O., and Roth, H. J.: Effects of novel antifungal azole derivatives on the 5-lipoxygenase and cyclooxygenase pathway. Drug Res. 40:1260, 1990.

Conjunctival Lymphocytic Nodule Associated With the Epstein-Barr Virus

Bradley P. Gardner, M.D., Todd P. Margolis, M.D., and Bartly J. Mondino, M.D.

Infection with Epstein-Barr virus has been reported to have numerous systemic and ocular manifestations. In this study, a 38-year-old man with acute infectious mononucleosis was examined for a painless left red eye of three days' duration. The patient had a two-week history of fatigue, low-grade fever, sore throat, and lymphadenopathy. Serologic evaluation was indicative of an acute primary infection with Epstein-Barr virus. A large, salmon-colored, supranasal bulbar conjunctival mass was observed in the left eye. No associated conjunctivitis was present. Biopsy of the conjunctival lesion disclosed a dense leukocytic infiltrate, which consisted primarily of mature lymphocytes and plasma cells. Immunocytochemical evaluation of the tissue with monoclonal antisera disclosed Epstein-Barr latent membrane protein and nuclear protein 2 in a small fraction of the cells constituting the infiltrate. The conjunctival infiltrate resolved completely within one month, paralleling the regression of the patient's lymphadenopathy.

THE EPSTEIN-BARR VIRUS is a double-stranded DNA virus of the herpesvirus family that is capable of establishing latent infections in B lymphocytes. A prominent feature of this virus is its ability to induce lymphoid proliferation of these latently infected cells. The Epstein-Barr virus was first associated with infectious mononucleosis in 1968[1,2] and is now known to be the most common cause of this disease. It may also have a role in the pathogenesis of Burkitt's lymphoma,[3] nasopharyngeal carcinoma,[4] thymic carcinoma,[5] Sjögren's syndrome,[6,7] and rheumatoid arthritis.[8]

The most common ocular manifestation of acute Epstein-Barr virus infection is a mild, usually unilateral, transient follicular conjunctivitis, which is detected in 2% to 40% of cases.[9] However, cases of severe conjunctivitis that may become membranous have been described.[9] A wide spectrum of less commonly observed ocular manifestations have also been reported. These include keratitis,[10,11] episcleritis,[12] iritis,[13] dacryocystitis,[14] retinitis,[15,16] choroiditis,[13,17] optic neuritis,[15] ophthalmoplegia,[18,19] and Parinaud's oculoglandular syndrome.[20]

We studied a patient with acute infectious mononucleosis who had a salmon-colored, bulbar conjunctival mass at initial examination. Pathologic examination disclosed a leukocytic infiltrate that was composed primarily of lymphocytes, some of which were positive for Epstein-Barr latent membrane protein and nuclear protein 2.

Case Report

A previously healthy 38-year-old man with acute infectious mononucleosis was referred for examination of a painless left red eye of three days' duration. He had a two-week history of generalized fatigue, low-grade fever, sore throat, and lymphadenopathy.

On ocular examination, the visual acuity was 20/15 in both eyes. Palpation disclosed enlarged, tender, and mobile left preauricular and submandibular lymph nodes (1 and 4 cm, respectively). A 1 × 2-cm salmon-colored, supranasal, bulbar conjunctival mass was observed in the left eye (Fig. 1). The lesion was movable over the sclera and nontender to palpation. The globe was not displaced, retropulsion was nor-

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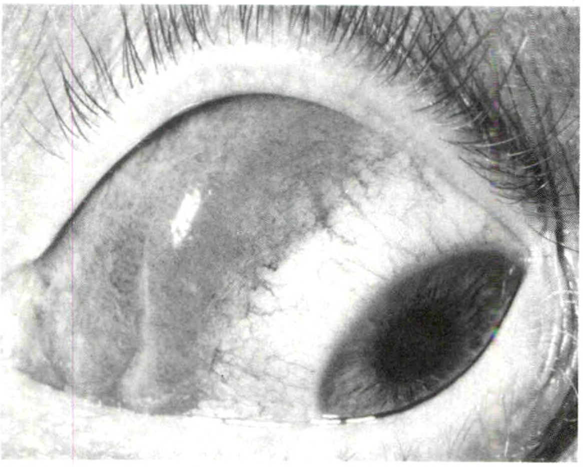

Fig. 1 (Gardner, Margolis, and Mondino). Conjunctival lymphocytic infiltrate at initial examination.

mal, and versions were full. The pupils were reactive without an afferent pupillary defect and visual fields were full. Conjunctivitis, keratitis, or discharge were not associated with the condition. The intraocular pressure was 14 mm Hg bilaterally and the fundus was clinically normal without evidence of uveitis or other lesions.

The patient had a packed-cell volume of 47.1%; blood platelet count of 276,000/mm^3; and white blood-cell count of 10,900/mm^3, 50% of which were atypical lymphocytes. The following liver enzyme concentrations were increased: alkaline phosphatase, 335 U/l; aspartate aminotransferase, 270 U/l; alanine aminotransferase, 692 U/l; and lactate dehydrogenase, 329 U/l. Total bilirubin concentration was 0.9 mg/dl. The Westergren sedimentation rate was 7 mm/hr. Results of the heterophil antibody test were positive. Serologic studies included a positive IgM titer (> 1:20) to the Epstein-Barr viral capsid antigen, and a negative IgG titer (< 1:5) to the Epstein-Barr nuclear antigen (Table). Results of thoracic radiography were normal. Abdominal ultrasonography demonstrated a normal-sized homogenous liver with mild splenomegaly. Fine-needle aspiration of the enlarged submandibular lymph node disclosed mixed reactive hyperplasia with numerous histiocytes. Lymphoma was not evident.

The conjunctival mass regressed in size by approximately 50% over the course of one week, and a biopsy was performed. Pathologic evaluation disclosed an extensive and dense leukocytic infiltrate, which consisted primarily of mature lymphocytes and plasma cells (Fig. 2). Scattered larger mononuclear cells and rare mitotic figures were observed. Immunofluorescence of the conjunctival biopsy specimen indicated the presence of Epstein-Barr latent membrane protein and nuclear protein 2 in the specimen (Fig. 3). By means of immunoperoxidase staining, these antigens were found to be associated with a small percent of the lymphocytic population of the infiltrate. Four sets of conjunctival controls (including two that were age-matched) failed to stain with either monospecific antiserum.

The conjunctival mass resolved completely over the next three weeks, paralleling the regression of the lymphadenopathy. Serologic evaluation at six months was positive for IgG titers to the Epstein-Barr virus capsid antigen (1:320) and the Epstein-Barr nuclear antigen (> 1:20). At one year, the IgG Epstein-Barr virus capsid antigen titer remained increased (1:160), but the IgM Epstein-Barr virus capsid antigen titer had decreased (< 1:20; Table). One year after the initial examination, the conjunctival lesion had not recurred.

TABLE
EPSTEIN-BARR VIRUS TITERS

ANTIGEN	JUNE 1990	DECEMBER 1990	MAY 1991
Viral capsid antigen			
IgM	>1:20	NP	<1:20
IgG	NP	1:320	1:160
Nuclear antigen			
IgG	<1:5	>1:20	1:5

NP indicates not performed.

Discussion

Primary Epstein-Barr viral infection in childhood is usually asymptomatic, but by late adolescence or early adulthood, primary infection with Epstein-Barr virus is commonly manifested as infectious mononucleosis. Clinical features of infectious mononucleosis include the classic triad of fever, sore throat, and lymphadenopathy. Hepatosplenomegaly is commonly observed as well. A relative and absolute lymphocytosis develops in 70% of patients and up to 90% of the lymphocytes may be atypical.[21]

The heterophil antibody test (Monospot test)

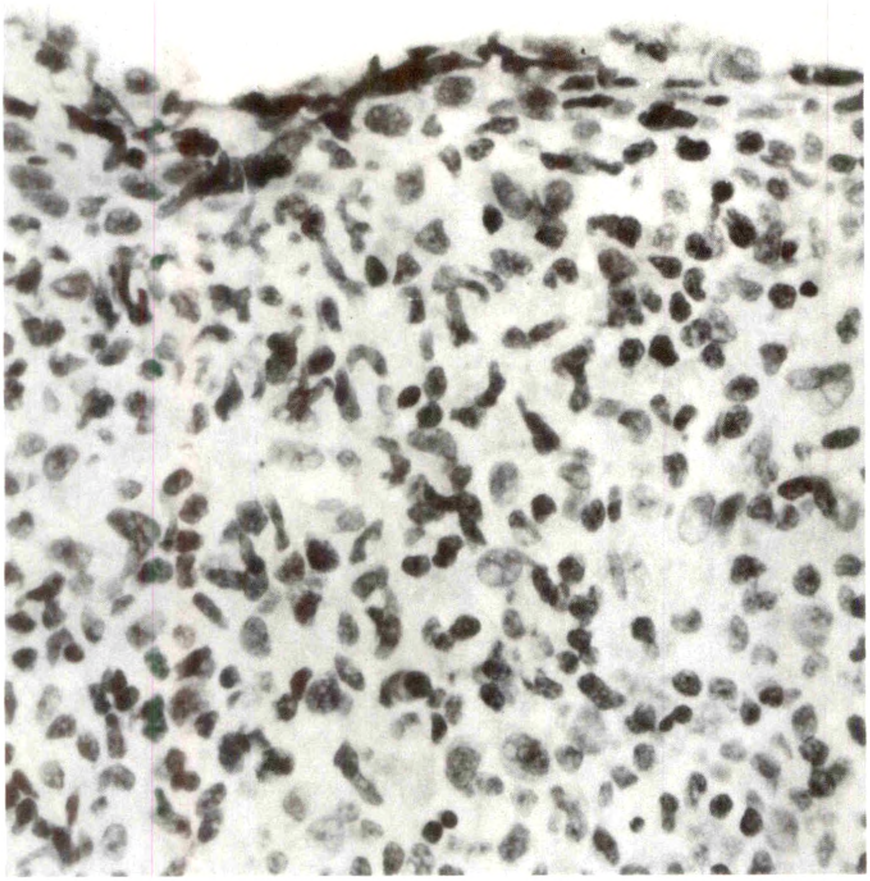

Fig. 2 (Gardner, Margolis, and Mondino). Histologic section of the lesion disclosing a dense leukocytic infiltrate consisting primarily of mature lymphocytes and plasma cells (hematoxylin and eosin, × 400).

is a rapid slide agglutination test for the serodiagnosis of infectious mononucleosis with a false-positive rate of less than 3%.[22] More specific serodiagnosis, however, is indicated in atypical clinical manifestations. The specific serodiagnosis of acute infectious mononucleosis is established by detection of high acute-phase IgM or IgG titers to the Epstein-Barr virus capsid antigen in the absence of positive titers to the Epstein-Barr nuclear antigen.[22] The diagnosis can be confirmed in convalescent serum samples by the demonstration of a decreased IgM titer to the Epstein-Barr virus capsid antigen and the emergence of anti-Epstein-Barr nuclear antigen antibodies. Our clinical and laboratory findings were therefore consistent with the diagnosis of an acute primary systemic infection with the Epstein-Barr virus.

Patients with Epstein-Barr virus lymphoproliferative disease may have polyclonal, oligoclonal, or monoclonal lymphocyte proliferation infiltrating lymph nodes or other tissues. These lymphocytes contain Epstein-Barr virus DNA and express specific Epstein-Barr virus proteins. Six different Epstein-Barr viral nuclear proteins and a membrane protein are expressed in B lymphocytes proliferating in vitro in response to latent Epstein-Barr viral infection.[23] Two of these proteins, Epstein-Barr nuclear protein 2 and latent membrane protein affect the growth of human B lymphocytes. Epstein-Barr nuclear protein 2 induces the expression of the B-cell activation antigen CD23, and latent membrane protein causes an increase in several B-lymphocyte activation and adhesion molecules, including ICAM 1 and LFA 3. Recently, Young and associates[23] demonstrated the usefulness of monoclonal antibodies to Epstein-Barr nuclear protein 2 and latent membrane protein in the early pathologic diagnosis of Epstein-Barr virus lymphoproliferative disease. Because immunocytochemical evidence of both Epstein-Barr nuclear protein 2 and latent membrane protein was found in the conjunctival

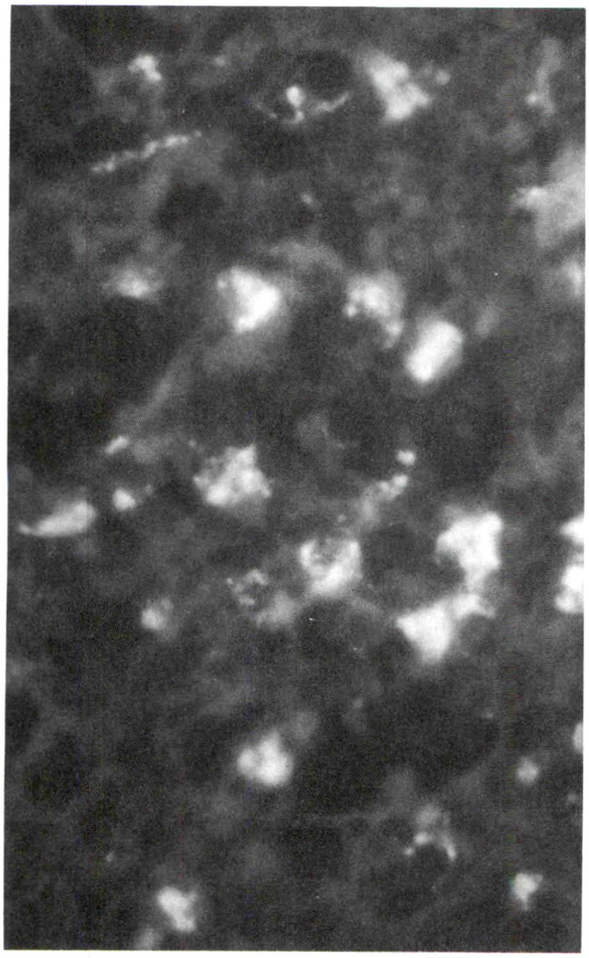

Fig. 3 (Gardner, Margolis, and Mondino). Biopsy specimen with monoclonal antisera for Epstein-Barr latent membrane protein demonstrating positive fluorescence (× 900).

biopsy specimen from our patient, it is likely that the Epstein-Barr virus was the causal agent of this localized lymphocytic infiltrate.

The kinetics of the appearance and disappearance of the conjunctival infiltrate are also consistent with a diagnosis of Epstein-Barr virus-related lymphoproliferation. The conjunctival mass was first observed 11 days after the onset of systemic symptoms and coincident with the onset of preauricular and submandibular lymphadenopathy. Similarly, resolution of the mass paralleled the course of resolution of the preauricular and submandibular lymphadenopathy (50% reduction in size over one week and complete resolution within one month). These findings are all consistent with the generally self-limited nature of infectious mononucleosis.

In 1981, Meisler, Bosworth, and Krachmer[20] reported a case of Parinaud's oculoglandular syndrome in an 11-year-old boy with a serologic profile consistent with an acute Epstein-Barr viral infection. The patient had unilateral conjunctivitis associated with a mild mucopurulent discharge, regional preauricular and cervical lymphadenopathy, and an inflamed nodular mass involving the superior palpebral conjunctiva at initial examination. Pathologically, the lesion consisted of mature and immature lymphoid cells heavily infiltrated in a perivascular distribution with many foci of necrosis. This was consistent with previous pathologic descriptions of infectious mononucleosis.[9,24] Additionally, the lesion contained fibrous tissue and intermittent multinucleated cells. Our case differed from that described by Meisler, Bosworth, and Krachmer[20] in several respects. First, conjunctivitis was not present in our case. Second, the lesion primarily involved the bulbar conjunctiva, not the palpebral conjunctiva in our patient. And third, pathologic findings were substantially different in our case; fibrous tissue was not a prominent feature; diffuse, not perivascular, infiltration was observed; and neither multinucleated giant cells nor areas of necrosis were found. Furthermore, immunocytochemical staining was performed in our case and confirmed the presence of Epstein-Barr viral antigens.

The lymphohistiocytic infiltrate in our case was benign and reactive as determined by clinical and histologic examination. However, Knowles and associates[25] have studied extranodal noncutaneous lymphoid hyperplasia of the ocular adnexa, and their results suggest that monoclonal B-cell populations may frequently develop within tissue otherwise meeting the histopathologic and immunophenotypic criteria for benign lymphoid hyperplasia. It is interesting that none of the cases of lymphoid neoplasia in the study of Knowles and associates[25] contained Epstein-Barr viral DNA sequences. Nonetheless, the Epstein-Barr virus has been linked to lymphoid neoplasia. Monoclonal and polyclonal malignant lymphomas have been reported in association with the Epstein-Barr virus in children with primary immunodeficiencies and in one case in an immunocompetent host.[26-28] Thus, patients with persistent Epstein-Barr virus-related lymphoproliferation should be carefully monitored.

References

1. Henle, G., Henle, W., and Diehl, V.: Relation of Burkitt's tumor-associated Herpes-type virus to in-

fectious mononucleosis. Proc. Natl. Acad. Sci. U.S.A. 59:94, 1968.

2. Niederman, J. C., McCollum, R. W., Henle, G., and Henle, W.: Infectious mononucleosis. Clinical manifestations in relation to EB virus antibodies. JAMA 203:205, 1968.

3. Lenoir, G. M.: Role of the virus, chromosomal translocations and cellular oncogenes in the etiology of Burkitt's lymphoma. In Epstein, M. W., and Achong, B. G. (eds.): The Epstein-Barr Virus. Recent Advances. New York, John Wiley and Sons, 1986, pp. 184–207.

4. Henle, G., and Henle, W.: Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carcinoma. Int. J. Cancer 17:1, 1976.

5. Leyvraz, S., Henle, W., Chahinian, A. P., Perlman, C., Klein, G., Gordon, R. E., Rosenblum, M., and Holland, J. F.: Association of Epstein-Barr virus with thymic carcinoma. N. Engl. J. Med. 312:1296, 1985.

6. Pflugfelder, S. C., Roussel, T. J., and Culbertson, W. W.: Primary Sjögren's syndrome after infectious mononucleosis. JAMA 257:1049, 1987.

7. Pflugfelder, S. C., Tseng, S. C. G., Pepose, J. S., Fletcher, M. A., Klimas, N., and Feuer, W.: Epstein-Barr virus infection and immunologic dysfunction in patients with aqueous tear deficiency. Ophthalmology 97:313, 1990.

8. Alspaugh, M. A., Jensen, P. C., Rabin, H., and Tan, E. M.: Lymphocytes transformed by Epstein-Barr virus. Induction of nuclear antigen reactive with antibody in rheumatoid arthritis. J. Exp. Med. 147:1018, 1978.

9. Tanner, O. R.: Ocular manifestations of infectious mononucleosis. Arch. Ophthalmol. 51:229, 1952.

10. Matoba, A. Y., Wilhelmus, K. R., and Jones, D. B.: Epstein-Barr viral stromal keratitis. Ophthalmology 93:746, 1986.

11. Matoba, A. Y., and Jones, D. B.: Corneal subepithelial infiltrates associated with systemic Epstein-Barr viral infection. Ophthalmology 94:1669, 1987.

12. Librach, I. M.: Ocular symptoms in glandular fever. Br. J. Ophthalmol. 40:619, 1956.

13. Wong, K. W., D'Amico, D. J., Hedges, T. R., Soeng, H. K., Schooley, R. T., and Kenyon, K. R.: Ocular involvement associated with chronic Epstein-Barr virus disease. Arch. Ophthalmol. 105:788, 1987.

14. Atkinson, P. L., Ansons, A. M., and Patterson, A.: Infectious mononucleosis presenting as bilateral acute dacryocystitis. Br. J. Ophthalmol. 74:750, 1990.

15. Karpe, G., and Wising, P.: Retinal changes with acute reduction of vision as initial symptoms of infectious mononucleosis. Acta Ophthalmol. 26:19, 1948.

16. Raymond, L. A., Wilson, C. A., Linnemann, C. C., Jr., Ward, M. A., Bernstein, D. I., and Love, D. C.: Punctate outer retinitis in acute Epstein-Barr virus infection. Am. J. Ophthalmol. 104:424, 1987.

17. Tiedeman, J. S.: Epstein-Barr viral antibodies in multifocal choroiditis and panuveitis. Am. J. Ophthalmol. 103:659, 1987.

18. Davie, J. C., Ceballos, R., and Little, S. C.: Infectious mononucleosis with fatal neuronitis. Arch. Neurol. 9:265, 1963.

19. Nelhaus, G.: Isolated oculomotor nerve palsy in infectious mononucleosis. Neurology 16:221, 1966.

20. Meisler, D. M., Bosworth, D. E., and Krachmer, J. H.: Ocular infectious mononucleosis manifested as Parinaud's oculoglandular syndrome. Am. J. Ophthalmol. 92:722, 1981.

21. Benson, C. A., and Kessler, H. A.: Update. Epstein-Barr virus-related disease. Compr. Ther. 14:58, 1988.

22. Henle, W., and Henle, G.: Serodiagnosis of infectious mononucleosis. Resident Staff Phys. 27:37, 1981.

23. Young, L., Alfieri, C., Hennessy, K., Evans, H., O'Hara, C., Anderson, K. C., Ritz, J., Shapiro, R. S., Rickinson, A., Kieff, E., and Cohen, J. I.: Expression of Epstein-Barr virus transformation-associated genes in tissues of patients with EBV lymphoproliferative disease. N. Engl. J. Med. 321:1080, 1989.

24. Jones, B. R.: Acute retinal periphlebitis associated with infectious mononucleosis. Trans. Ophthalmol. Soc. U.K. 74:119, 1954.

25. Knowles, D. M., Athan, E., Ubriaco, A., McNally, L., Inghirami, G., Wieczorek, R., Finfer, M., and Jakobiec, F. A.: Extranodal noncutaneous lymphoid hyperplasias represent a continuous spectrum of B-cell neoplasia. Demonstration by molecular genetic analysis. Blood 73:1635, 1989.

26. Robinson, J. E., Brown, N., Andiman, W., Halliday, K., Franke, U., Robert, M., Andersson-Anvert, M., Horstmann, D., and Miller, G.: Diffuse polyclonal B-cell lymphoma during primary infection with Epstein-Barr virus. N. Engl. J. Med. 302:1293, 1980.

27. Morgan-Capner, P., Morris, J. A., McIllmurray, M. B., Thomas, J. A., Crawford, D. H., and Azim, T.: Immunohistological studies of lymphoproliferative lesions in a fatal case of Epstein-Barr virus infection. J. Clin. Pathol. 39:1317, 1986.

28. Pattengale, P. K., Taylor, C. R., and Pegalow, C.: Malignant B-cell lymphoma following and associated with infectious mononucleosis. A comparison of two cases. Am. J. Pediatr. Hematol. Oncol. 3:35, 1981.

A Sibship With Unusual Anomalies of the Eye and Skeleton (Michels' Syndrome)

Monica A. De La Paz, M.D., Richard Alan Lewis, M.D., James R. Patrinely, M.D., Lawrence Merin, and Frank Greenberg, M.D.

Four siblings of nonconsanguineous parents had congenital anomalies of the anterior segment of the eyes, eyelids, and skeletal systems. Anomalies of the anterior segment included opacities of the corneal stroma, conjunctival telangiectasia, and iridocorneal adhesions. Eyelid abnormalities included blepharoptosis, blepharophimosis, and telecanthus. One sibling with extensive anterior segment anomalies developed glaucoma. All subjects had impaired vertical gaze. Oromandibular anomalies varied from cleft lip and palate to malocclusion with overbite. Additional features included subnormal intelligence, short stature, hearing loss, and clinodactyly. This spectrum of anomalies appeared to have been transmitted as an autosomal recessive syndrome.

THE SIBSHIP OF nonconsanguineous parents in which four of six surviving siblings had multiple congenital ocular and systemic anomalies was originally reported in 1978,[1] but numerous additional features have been identified. Members of this sibship appeared to have a unique genetic syndrome, which was described only partially in the previous report.

Case Reports

Of seven siblings, four were affected with an unusual spectrum of congenital anomalies (Fig. 1). The parents were of Mexican descent and were not known to be related. Their families came from different regions of the country. No previous family history of either ocular or facial anomalies was known. The parents were 21 and 18 years of age at the time of birth of their first affected child. No history of maternal infection or use of alcohol or other embryopathic drugs during any pregnancy exists. There was a history of maternal exposure to rubella without clinical signs of disease at three months' gestation of the eldest male child (Case 1, III-3).

Results of physical and ocular examinations of the parents were remarkable only for mild type-I syndactyly of the second and third toes in the father. The firstborn child was normal physically and died at 3 months of age of an apparent crib death. No other details were available. Two siblings (III-2, III-6) were unaf-

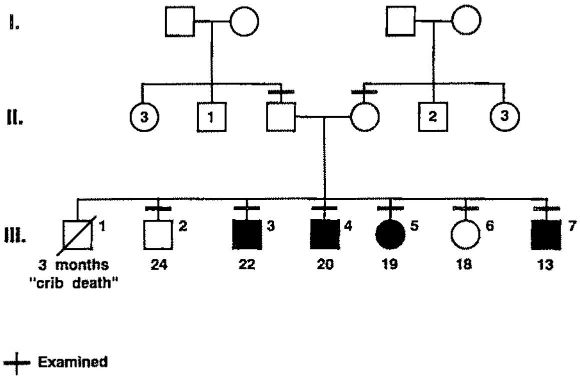

Fig. 1 (De La Paz and associates). Pedigree of affected kinship. The inheritance pattern suggests an autosomal recessive disorder. Ages at time of examination are shown.

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fected. The pedigree (Fig. 1) differs from the original report, which did not mention the first-born child or the unaffected male sibling.

Case 1 (III-3)

The eldest affected male child was born after an uncomplicated pregnancy and was delivered at full term. Physical examination at birth disclosed bilateral cleft lip and cleft palate. The cleft lip was repaired at 3 years of age and the cleft palate was repaired at 4 years of age. A childhood history of recurrent middle ear infections and bilateral conductive hearing loss with a sensorineural component above 4,000 Hz was found. Malocclusion was managed with a maxillary prosthesis. Spectacles for correction of severe hyperopia were worn since the age of 8 years.

Physical examination at 22 years of age demonstrated a man of short stature and a dysmorphic facies characterized by nasal asymmetry with lateral displacement of the nasal dorsum to the right (Fig. 2). His height was 158 cm (< fifth percentile), his weight was 63 kg (25th percentile), his head circumference was 55 cm (25th percentile), and his foot length was 23 cm (third percentile). The border of the upper lip was scarred at the site of the repaired cleft lip. The eyebrows had exaggerated arches, which were in part related to the patient's effort to minimize blepharoptosis. Vertical ear lengths were asymmetric; the right ear measured 6 cm and the left measured 7 cm.

His best-corrected visual acuity was R.E.: 20/60 (+10.50 sph) and L.E.: 20/100 (+8.75 sph). External examination disclosed telecanthus with an intermedial canthal distance of 40 mm (> 97th percentile), an interpupillary distance of 68 mm (> 97th percentile), and an interlateral canthal distance of 90 mm (60th percentile). The horizontal palpebral fissures each measured 25 mm (20th percentile). Bilateral epicanthus inversus and moderate blepharoptosis were observed. The vertical palpebral fissures of each eye measured 5 mm (Fig. 2). The function of the levator palpebrae superioris muscle of each eye measured 1 mm. An intermittent alternating exotropia of 30 prism diopters was associated with marked limitation of upgaze and downgaze of each eye; results of forced duction testing were negative. Horizontal jerk nystagmus was observed in primary gaze and increased in amplitude in the extremes of gaze. The amplitude increased when either eye was covered. Horizontal corneal diameters of each eye measured 10 mm. Large, superior corneal opacities involving the deep stroma and Descemet's membrane extended downward into the visual axis of each eye (Fig. 3). Bilateral prominent superior telangiectatic episcleral vessels were also observed. Gonioscopy disclosed high insertion of the iris stroma into the trabecular meshwork and iris strands attached to the endothelial surface of the superior corneal opacities in each eye. The remaining results of ophthalmic examination were normal, including intraocular pressures of 20 mm Hg in each eye.

The patient had an IQ of 60 (Wechsler Intelligence Scale for Children—Revised). He had attended special education classes through the age of 18 years. His speech was hypernasal with a quality suggestive of velopharyngeal insufficiency. Radiographs of the skull showed no abnormality of the sinuses. Results of a Giemsa-banded karyotype (200 to 400 band length) in 1977 were normal.

Case 2 (III-4)

A male was born with a cleft lip and palate, which was repaired at 18 months of age and repaired again at 20 years of age. Recurrent middle ear infections in childhood were presumed to have caused a moderate bilateral conductive hearing loss. Spectacles for correction of myopic astigmatism had been worn since the age of 7 years.

At 20 years of age, anthropometry determined his height to be 158 cm (< fifth percentile), his weight to be 54 kg (< fifth percentile), and his head circumference to be 55 cm (tenth percentile). Mild facial asymmetry was accentuated by high-arched eyebrows and flattening of the right lower face. The arching of the eyebrows was exacerbated by his attempts to minimize blepharoptosis. The lengths of both ears and hands were normal.

The best-corrected visual acuity was R.E.: 20/20 (−2.25 + 2.50 × 90 degrees) and L.E.: 20/25 (−2.50 + 4.50 × 105 degrees). The external examination showed epicanthus inversus and moderate bilateral blepharoptosis (Fig. 2). Vertical palpebral fissures of each eye measured 5 mm. The function of the levator palpebrae superioris of the right eyelid was 1 mm but no function was elicited from the left. Motility examination disclosed marked impairment of both upgaze and downgaze of each eye. Results of forced duction testing were negative. The horizontal corneal diameters were 10.5 mm bilaterally. Vascularized corneal opacities and bilateral superior episcleral telangiectasia were

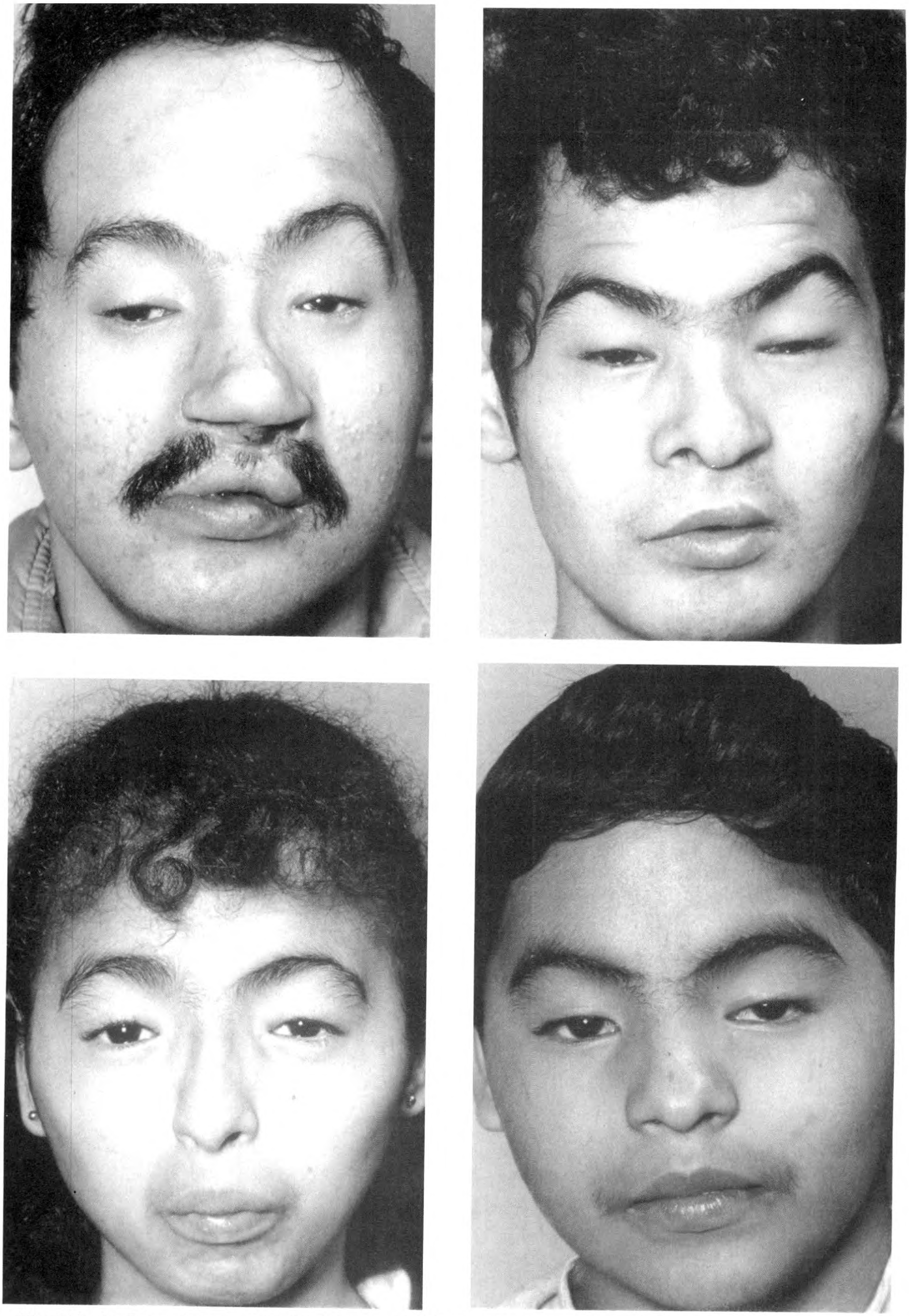

Fig. 2 (De La Paz and associates). Top left, Case 1 (III-3), age 22 years. Top right, Case 2 (III-4), age 20 years. Bottom left, Case 3 (III-5), age 19 years. Bottom right, Case 4 (III-7), age 13 years. Similar dysmorphic facial features are shown and include blepharoptosis, blepharophimosis, and telecanthus.

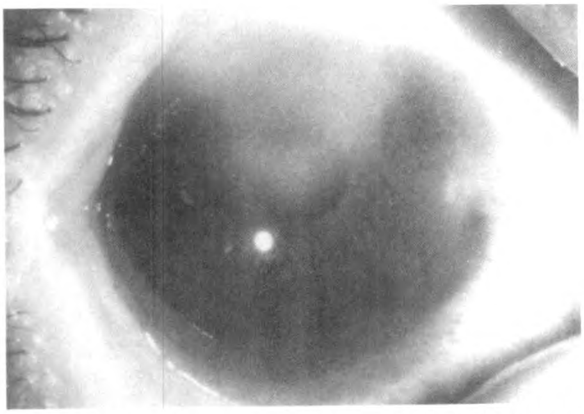

Fig. 3 (De La Paz and associates). Case 1. Right eye demonstrates wedge-shaped superior corneal opacity. A similar finding was observed in left eye.

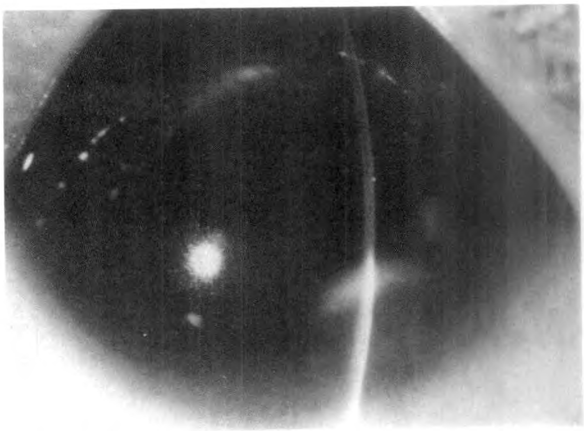

Fig. 4 (De La Paz and associates). Case 2. Right eye demonstrates an inferior wedge-shaped corneal opacity.

observed in the inferonasal periphery of the right eye and the superior periphery of the left eye (Fig. 4). Iris strands to the endothelial surface were observed in the region of the corneal opacification in the left eye. Intraocular pressures by applanation were 20 mm Hg and 21 mm Hg in the right and left eyes, respectively. General physical examination exhibited both brachydactyly and clinodactyly of the fifth digits of each hand.

This patient, who also had attended special education classes, had an IQ of 80 (Wechsler Intelligence Scale for Children—Revised). His moderately hypernasal speech was consistent with velopharyngeal insufficiency. Radiographs of the skull showed no abnormality of the sinuses. Results of a Giemsa-banded karyotype were normal.

Case 3 (III-5)

The only affected female in the sibship had moderate conductive hearing loss through 2,000 Hz of the right ear and mild conductive impairment of the left ear. Severe malocclusion with a right cephalad tilt to her occlusal plane was observed. Spectacles for correction of myopic astigmatism had been worn since 4 years of age and she had had occlusion therapy for amblyopia at the age of 7 years.

At the age of 19 years, the patient was a well-developed woman who was 154 cm in height (fifth percentile), 43 kg in weight (< fifth percentile), and had a head circumference of 52 cm (< fifth percentile). Her foot length was 22 cm (15th percentile). The facies was mildly asymmetric with flattening of the right side (Fig. 2). Her mandible had an abnormal configuration with an obtuse angle, suggestive of mandibular hypoplasia. The hard palate was arched without a cleft or indention and her teeth were crowded. Her ear and hand lengths were normal. The fifth fingers of both hands showed brachydactyly and clinodactyly. Supination and pronation of her forearms was limited bilaterally by radioulnar synostosis.

Best-corrected visual acuity was R.E.: 20/20 (−2.75 + 1.75 × 105 degrees) and L.E.: 20/50 (−1.75 + 4.75 × 80degrees). Moderate blepharoptosis and bilateral epicanthus inversus were observed. Vertical palpebral fissures of each eye measured 6 mm, and function of the levator palpebrae superioris muscle measured 2 mm on the right but no function was elicited on the left. The intermedial canthal distance was 40 mm (> 97th percentile), the interpupillary distance was 60 mm (80th percentile), the interlateral canthal distance was 90 mm (60th percentile), and both horizontal palpebral fissures measured 25 mm in length (tenth percentile). Both upgaze and downgaze of each eye were markedly impaired, but results of forced duction testing were negative. The horizontal corneal diameters of each eye measured 11 mm. The right cornea was normal, but the left had a superior peripheral opacification of the deep stroma and Descemet's membrane (Fig. 5). The iris stroma inserted high into the trabecular meshwork; uveal pigment was observed on the endothelial surface of the corneal opacity. Intraocular pressures by applanation were 20 mm Hg and 19 mm Hg in the right and left eyes, respectively. Intelligence and speech were normal.

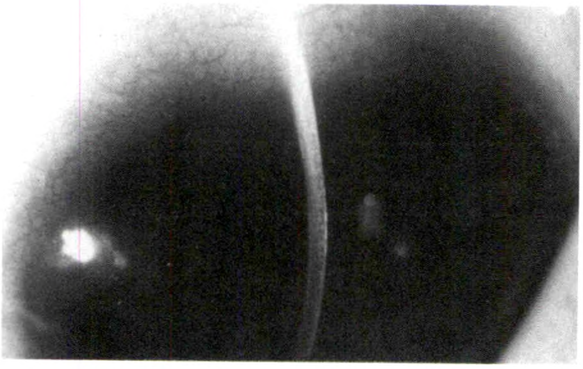

Fig. 5 (De La Paz and associates). Case 3. Left eye demonstrates peripheral corneal opacity.

Case 4 (III-7)

The youngest of the affected siblings had a small omphalocele repaired shortly after birth. A urethral stricture was repaired at 6 months of age. He had recurrent otitis media and had used a hearing aid in the right ear since the age of 7 years. He had worn spectacles for correction of hypermetropic astigmatism since the age of 3 years.

On physical examination at 13 years of age, this well-developed boy was 145.5 cm tall (tenth percentile), weighed 47 kg (50th percentile), and had a head circumference of 53.5 cm (25th percentile). The right side of his face was flattened and asymmetric. Synophrys and arched eyebrows were observed (Fig. 2), but the ear lengths were normal. His right hand length measured 17.5 cm on the right (60th percentile) and 16.0 cm on the left (20th percentile). Bilateral brachydactyly of the fifth digits of the hands and bilateral radioulnar synostosis were observed.

His best-corrected visual acuity was R.E.: 20/30 (+2.75 + 3.25 × 105 degrees) and L.E.: 20/50 (+2.75 + 3.75 × 85 degrees). Bilateral epicanthus inversus and mild blepharoptosis were associated with vertical palpebral fissures of 8 mm in the right eye and 7 mm in the left eye. The vertical function of the levator palpebrae superioris muscle of both eyes was 1 mm. The intermedial canthal distance measured 35 mm (97th percentile), interpupillary distance was 60 mm (80th percentile), interlateral canthal distance was 91 mm (60th percentile), and horizontal palpebral fissures were 28 mm (75th percentile). Both upgaze and downgaze were severely impaired and results of forced duction tests were mildly positive in both up and down directions. Bilateral superior wedge-shaped corneal opacities and superior telangiectatic episcleral vessels were observed (Fig. 6). The corneal diameters of the right and left eyes were 11.5 mm and 11.0 mm, respectively. The hypoplastic iris root in each eye inserted high into the trabecular meshwork with numerous iris strands to Schwalbe's line (Fig. 7). Peripheral iridocorneal adhesions were also observed in the left eye. The intraocular pressures by applanation were 48 mm Hg and 32 mm Hg in the right and left eyes, respectively. Goldmann perimetry disclosed an inferior arcuate scotoma of the right eye and no abnormalities of the left eye. The optic disks had mild cup-to-disk asymmetry and an increase in vertical diameter of the right eye (Fig. 8). The retinal vasculature had numerous anomalous retinal vessels with early branching and several vascular loops on the optic disk in each eye. The increased intraocular pressure responded to a topical adrenergic inhibitor.

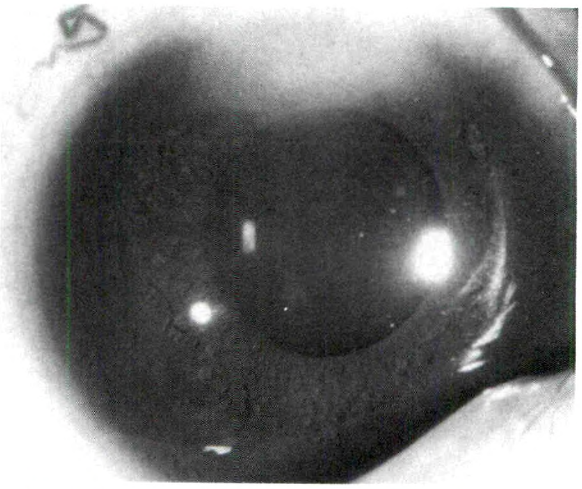

Fig. 6 (De La Paz and associates). Case 4. Findings in the anterior segment of the right eye include corneal opacities and telangiectatic episcleral vessels. Corneal opacities are at the level of the stroma and Descemet's membrane.

Intelligence was normal. His speech resembled that of his siblings. Results of a high-resolution Giemsa-banded chromosome analysis were normal at 13 years of age.

A laboratory examination of all affected siblings included serum electrolytes, calcium, complete blood cell count, urinalysis, and serum and urinary amino acids; all results were normal.

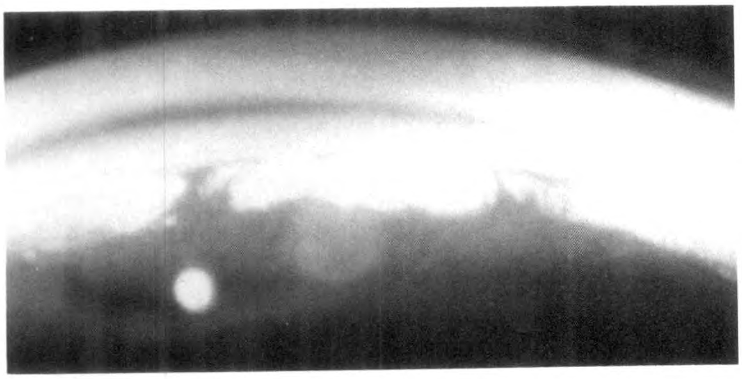

Fig. 7 (De La Paz and associates). Case 4. Anterior chamber angle. Prominent iris strands are seen extending to Schwalbe's line.

Discussion

The affected members of the sibship shared the constellation of congenital anomalies of unusual facies, oromandibular abnormalities, hearing deficits, hypernasal speech, blepharoptosis, blepharophimosis, telecanthus, epicanthus inversus, peripheral corneal opacities with adjacent telangiectatic episcleral vessels, abnormal peripheral irides, and bilateral restriction of upgaze and downgaze. Additional features comprised small head circumference, short stature, facial asymmetry, small feet, and brachydactyly and clinodactyly of the fifth digits of the hands. Inconsistent but common anomalies included intellectual delay, cleft lip and palate, microcornea, refractive amblyopia, and radioulnar synostosis. The original report[1] emphasized the corneal opacities and the eyelid anomalies. Anomalies unreported previously include malocclusion, refractive amblyopia, microcornea, glaucoma, high insertion of the iris stroma into the trabecular meshwork, and a restrictive vertical gaze deficit involving both upgaze and downgaze. The patient described as Case 1, apparently the most severely affected, also had nystagmus, intermittent exotropia, and severe hypermetropia. In Case 4, the patient had prominent anterior segment anoma-

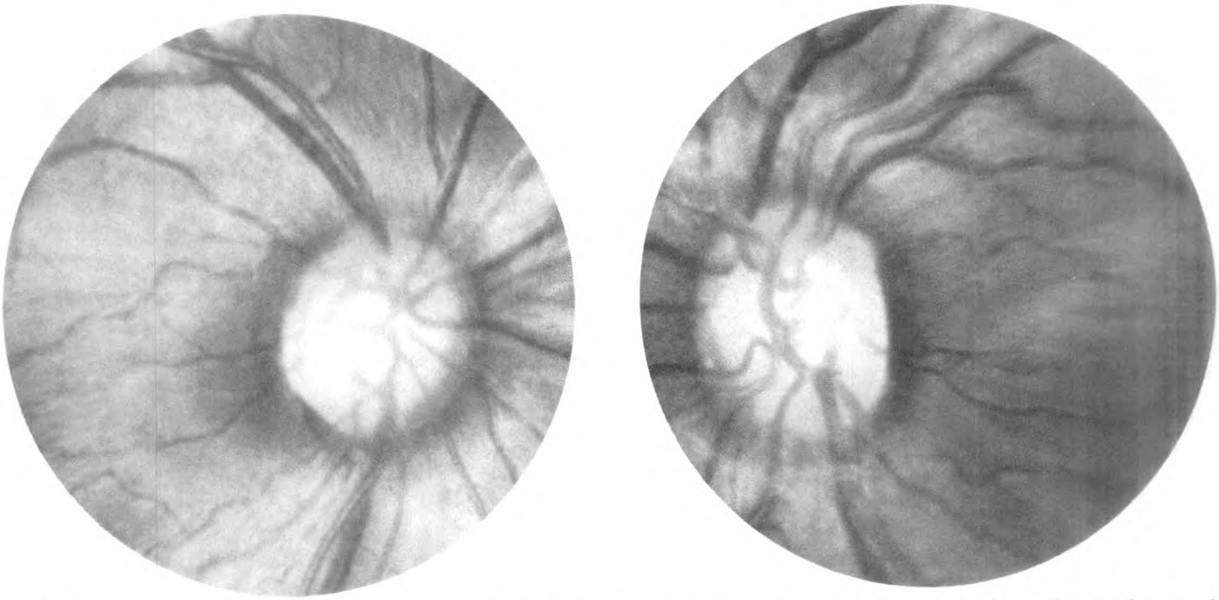

Fig. 8 (De La Paz and associates). Case 4. Prominent cupping and early anomalous branching of retinal vasculature are visible.

lies and had developed glaucoma. Other affected members of the sibship may be at risk for its development and will be monitored diligently. The pedigree analysis is most consistent with an autosomal recessive disorder. Results of chromosomal studies of each affected sibling were normal.

The facial features of the affected siblings were distinct. Variable expressivity of facial anomalies was suggested by the cleft lip and palate in two siblings, a high-arched palate in one sibling, and facial asymmetry alone in another. The maxillary and mandibular abnormalities, hearing deficits, eyelid anomalies, and segmental corneal opacities were reminiscent of a facial clefting syndrome.

Craniofacial clefts have been associated with many ocular anomalies.[2,3] Tessier[3] described microphthalmia in some clefts through the orbit, sometimes with nasal deformities including proboscis lateralis and metatrophy of the nose. In Case 1, with anomalies that included microcornea, high hyperopia, and a nasal deformity, the patient may have had a similar clefting disorder. Tessier did not mention associated corneal opacities.

The facial asymmetry of the affected siblings was not representative of hemifacial microsomia, a unilateral dysplasia involving the ear and face, with hypoplasia of the maxillary, malar, and palatine bones.[4,5] Hemifacial microsomia may have associated Horner's syndrome, oculomotor palsies, and nystagmus. However, our findings in this sibship included corneal opacities and the eyelid tetrad, not parts of hemifacial microsomia. Additionally, familial occurrence of hemifacial microsomia is uncommon.

The unusual facies of this sibship resembled some aspects of the Kabuki make-up or Niikawa-Kuroki syndrome,[6] a syndrome of multiple congenital anomalies described predominantly in Japanese children, in which the facial features are reminiscent of actors in Kabuki, the traditional Japanese theater. Craniofacial features include high-arched eyebrows, cleft or high-arched palate, and defective dentition. However, our affected siblings did not show eversion of the lower lateral eyelid, depressed nasal tip, or prominent ears. Except for strabismus, ocular anomalies are not usual components of the Kabuki make-up syndrome.

The various anterior segment anomalies in this sibship manifested primarily as wedge-shaped superior peripheral corneal opacities, adjacent telangiectatic episcleral vessels, and abnormal peripheral irides with iridocorneal adhesions. Two affected siblings had microcornea, and another had developed glaucoma. Developmental defects of the anterior segment have been associated with various ocular and systemic abnormalities. The Axenfeld-Rieger syndrome[7] may have various nonocular features in addition to juvenile glaucoma. However, eyelid anomalies and corneal opacities are not common features. Aniridia may have associated corneal opacities, blepharoptosis, and skeletal defects.[8-10] Yet, the appearance of the iris and the cornea and the lack of foveal hypoplasia in members of this sibship make that diagnosis unlikely.

The syndromic tetrad of blepharoptosis, blepharophimosis (narrowing of the interpalpebral fissure), epicanthus inversus, and telecanthus (widening of the intermedial canthal distance) may have a hypoactive levator palpebrae superioris muscle,[11-13] which did apply to this family. Underaction of both the superior and inferior recti muscles has been noted in some patients with this tetrad.[11] Anderson and Baumgartner[14] reported congenital blepharoptosis and underaction of both the superior and inferior recti muscles. In some instances this underaction manifests as a double elevator palsy. Although three of our four affected siblings had negative results of forced duction tests, the motility deficit of the single affected sibling with the positive results of forced duction tests resembles a bilateral double elevator palsy with contractures of the inferior rectus muscle. Results of all chromosomal studies of the blepharophimosis tetrad have been normal or unremarkable. This tetrad is autosomal dominant in inheritance, with almost complete penetrance.[11]

Anomalies of the eye and face are uncommon features of the blepharophimosis tetrad. Some reports mention the infrequent ocular features of microphthalmos, strabismus, amblyopia, orbital malformations, and nystagmus.[15-17] The cause of the nystagmus is not discussed. Although the time of clinical onset is not known definitely, the features of the nystagmus in Case 1 are consistent with an infantile variant from poor visual acuity caused by refractive amblyopia. A superimposed latent component is not uncommon in congenital nystagmus. Latent nystagmus is commonly associated with strabismus, which was also observed in Case 1.

Frontofacionasal dysplasia is an uncommon autosomal recessive syndrome of malformations of the midface described in three individuals, two of whom were siblings.[18] The main characteristics include severe midface hypoplasia, cleft lip and palate, nasal hypoplasia, S-shaped palpebral fissures, blepharophimosis, and telecanthus. Cataract, microcornea, and iris coloboma were observed in one affected individual. The two siblings had eyelid colobomata, and one had a limbal dermoid. Although some characteristics of this syndrome resembled those of our siblings, a number of important differences existed. The characteristic hypoplastic nasal anomalies and S-shaped eyelid margins described in all patients with frontofacionasal dysplasia were not observed in any of the four affected siblings of this report. Gaze abnormalities and vascularized corneal stromal opacities are not described in frontofacionasal dysplasia. Additionally, patients with this syndrome have no abnormalities outside of the craniofacial region, such as skeletal anomalies and subnormal intelligence. Rather, there is a trend toward more severe craniofacial anomalies, including brachycephaly and encephalocele, which were not observed in the affected siblings.

The Dubowitz syndrome is an autosomal recessive disorder originally described in 1965.[19] Characteristics include growth retardation and bone age delayed from chronologic age, microcephaly, broad forehead, telecanthus, blepharophimosis, abnormal pinnae, broad nose, and micrognathia. Cleft palate is uncommon. Anomalies of the anterior segment have not been mentioned. Additionally, although blepharophimosis is present, the facies differs substantially from that of our siblings.

Chondrodystrophic myotonia is an autosomal recessive syndrome that includes the features of dwarfism, multiple skeletal deformities, and myotonia.[20] Blepharophimosis and microcornea are inconsistent features. The lack of skeletal deformities and myotonia makes the diagnosis of chondrodystrophic myotonia unlikely in our four affected siblings.

Craniosynostosis, which was observed in two of the affected siblings (lambdoidal synostosis in Cases 1 and 4), has been previously described in a patient with the blepharophimosis tetrad.[21] The patient was a 2-year-old girl with coronal craniosynostosis and mental deficiency. However, unlike the siblings described in this report, oromandibular and ocular anomalies were not observed. Thus, it is unclear, if not unlikely, that the patient described by Cunniff and Jones[21] had the same syndrome as our family.

We believe that the constellation of congenital anomalies in this family represents a genetic syndrome that has been incompletely described and therefore unrecognized. The multiplicity of congenital anomalies in this sibship emphasizes the need for diligent and comprehensive investigation of individuals with developmental disorders of the eye and face.

References

1. Michels, V. V., Hittner, H. M., and Beaudet, A. L.: A clefting syndrome with ocular anterior chamber defect and lid anomalies. J. Pediatr. 93:444, 1978.
2. Dufresne, C. R., and Jelks, G. W.: Classification of craniofacial malformations. In Smith, B. C. (ed.): Ophthalmic Plastic and Reconstructive Surgery. St. Louis, The C. V. Mosby Co., 1987, pp. 1185–1207.
3. Tessier, P.: Anatomical classification of facial, cranio-facial, and latero-facial clefts. J. Maxillofac. Surg. 4:69, 1976.
4. Gorlin, R. J., Cohen, M. M., and Levin, L. S. (eds.): Branchial arch and oro-acral disorders. In Syndromes of the Head and Neck, ed. 3. New York, Oxford University Press, 1990, pp. 641–648.
5. Pico, G., and Townsend, W.: Congenital and developmental anomalies of the orbit. In Tasman, W., and Jaeger, E. A. (eds.): Duane's Clinical Ophthalmology, vol. 2. Philadelphia, J. B. Lippincott Co., 1989, p. 10.
6. Niikawa, N., and 45 associates: Kabuki make-up (Niikawa-Kuroki) syndrome. A study of 62 patients. Am. J. Med. Genet. 31:565, 1988.
7. Shields, M. B.: Developmental glaucomas with associated anomalies. In Textbook of Glaucoma. Baltimore, Williams & Wilkins Co., 1987, pp. 199–219.
8. David, R., MacBeath, L., and Jenkins, T.: Aniridia associated with microcornea and subluxated lenses. Br. J. Ophthalmol. 62:118, 1978.
9. Shields, M. B., and Reed, J. W.: Aniridia and congenital ptosis. Ann. Ophthalmol. 7:203, 1975.
10. Duke-Elder, S.: Normal and abnormal development. In System of Ophthalmology, vol. 3, pt. 2. St. Louis, The C. V. Mosby Co., 1963, p. 567.
11. Kohn, R., and Romano, P. E.: Blepharoptosis, blepharophimosis, epicanthus inversus, and telecanthus. A syndrome with no name. Am. J. Ophthalmol. 72:625, 1971.
12. Klein, M.: Hereditary bilateral ptosis and blepharophimosis associated with other develop-

mental abnormalities of the outer eye. Proc. R. Soc. Med. 43:1025, 1950.

13. Spaeth, E. B.: Further considerations on the surgical correction of blepharophimosis (epicanthus). Am. J. Ophthalmol. 41:61, 1956.

14. Anderson, R. L., and Baumgartner, S. A.: Strabismus in ptosis. Arch. Ophthalmol. 98:1062, 1980.

15. Fox, S. A.: Blepharophimosis. Am. J. Ophthalmol. 55:469, 1963.

16. McIllroy, J.: Hereditary ptosis with epicanthus. A case with a pedigree extending over four generations. Proc. R. Soc. Med. 23:285, 1930.

17. Owens, N., Hadley, R., and Kloepfer, R.: Hereditary blepharophimosis, ptosis, and epicanthus inversus. J. Int. Coll. Surg. 33:558, 1960.

18. Gollop, T. R., Kiota, M. M., Martina, R. M. M., Lucchesi, E. A., and Alvarenga, E.: Frontofacionasal dysplasia. Evidence for autosomal recessive inheritance. Am. J. Med. Genet. 19:301, 1984.

19. Moller, K. T., and Gorlin, R. J.: The Dubowitz syndrome. A retrospective. J. Craniofac. Genet. Dev. Biol. [Suppl.] 1:283, 1985.

20. Aberfeld, D. C.: Chondrodystrophic myotonia. In Bergsma, D. (ed.): Birth Defects Compendium, ed. 2. New York, Alan R. Liss, Inc., 1974, pp. 196–197.

21. Cunniff, C., and Jones, K. L.: Craniosynostosis and lid anomalies. Report of a girl with the Michels syndrome. Am. J. Med. Genet. 37:28, 1990.

OPHTHALMIC MINIATURE

At length she said sadly, ''Then it's over between us, Pilgrim Michael, and may this be the last time that I seek love. You'll soon forget me when our voyage is ended. Let us hope that I shall forget you as easily. For the love of God, Michael, don't look into my eyes. They are evil.''

I knew of course that there are people who without any malicious intent can injure others with their gaze. My teacher, Doctor Paracelsus, believed that the evil eye could cause a fruit tree to wither.

Mika Waltari, *The Wanderer*
New York, Pocket Books, 1957, p. 9

Unilateral Diplophthalmos

F. H. Stefani, M.D., N. Hausmann, M.D., and O.-E. Lund, M.D.

In a child born of a full-term pregnancy, unilateral diplophthalmos without proboscis was observed along with other craniocervical abnormalities (ipsilateral temporoparietal porencephaly, supernumerary teeth, and cervical cyst). A globe almost normal in shape and size was observed within the left orbit. The upper quadrant of this globe was attached to a smaller, pear-shaped, supernumerary eye containing a small lens, normal vitreous humor, ciliary body structures, avascular retina, choroid, and a rudimentary optic disk. When a two-peaked and enlarging intraocular mass was observed clinically, the eye was enucleated because of suspected neoplasm. The enlarging prominence had been caused by the growing second globe. Our findings indicated that a single primary optic vesicle was formed (globe I with an optic fasciculus), and some unknown damage was caused when this single primary optic vesicle induced the lens formation by contacting the ectoderm. Although the conception and early embryonal life of this child had taken place during a period of increased radiation exposure caused by the explosion of the nuclear plant at Chernobyl, U.S.S.R., in the spring of 1986, it seemed unlikely that the abnormality could have been caused by radioactive fallout in the mountains of Austria.

CYCLOPIA with a median single eye or two fused eyes is uncommon in humans and is usually associated with gross deformities of the skull and the neuronasal apparatus. A supernumerary eye is even more uncommon. Duplication of eyes develops in unilateral cyclopia or synophthalmos and usually involves a lateral proboscis. These eyes may have two corneas or two retinas. This anomaly is regarded as a failure of separation of monozygous twins.

Case Report

Clinical history—A healthy woman (gravida 4) had a healthy son from her first pregnancy in 1983. Several members of her family have diabetes mellitus and her husband has a clubfoot. She had two further pregnancies with one stillborn dystrophic infant and a fifth-month intrauterine death. Her most recent pregnancy was unremarkable. A mature female infant was born at Week 39 of gestation in April 1987. Asymmetry of the skull was noticed immediately after birth. A localized, left-sided congenital arachnoidal cyst that communicated with the third ventricle and formed a localized left-sided internal hydrocephalus was diagnosed and treated surgically with a ventriculoatrial Holter-Hausner shunt. Additionally, a left-sided lateral cervical 1-cm cyst was removed. One month later, the left optic disk seemed to have a discrete pallor. When the child was 4 months old, blue sclerectasia, which might have been overlooked previously, was noticed at the 2 o'clock position of the left eye (Fig. 1). Ophthalmoscopically, a disk-shaped solid intraocular prominence resembling a tumor was observed and a flat retinal detachment was suspected. Ultrasonography disclosed high reflectivity and hemangioma was diagnosed. By the age of 9 months, the mass had decreased in size, but had developed two peaks and its edges showed yellow-white subretinal material. Retinal detachment was no longer visible. When she was 21 months old, the left eye lacked abduction but the sclerectasia had not changed. Ophthalmoscopically, a large mushroom-shaped intraocular mass with slight adjacent retinal detach-

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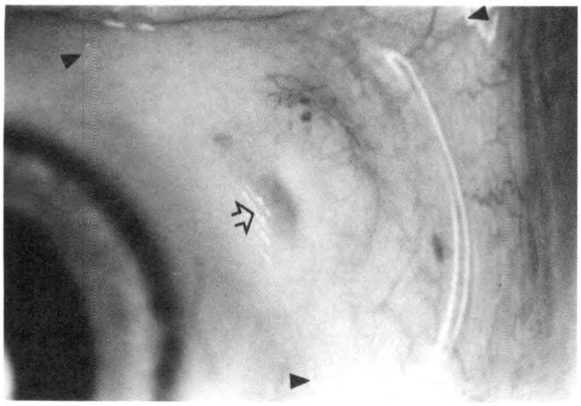

Fig. 1 (Stefani, Hausmann, and Lund). Clinical appearance of the left eye. The scleral staphylomatous swelling is marked by closed triangles and the corneal window showing the iris with the pupil is marked by an open arrow.

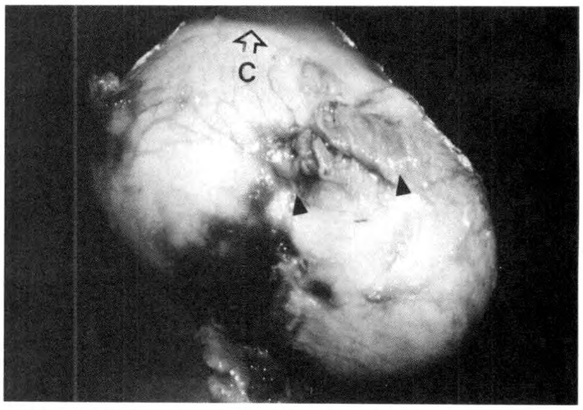

Fig. 2 (Stefani, Hausmann, and Lund). Macroscopic outer appearance of the gross specimen. C indicates cornea of regular main globe I on the left and the extra globe II on the right. Closed triangles mark the scleral insertion site of the lower rectus muscle.

ment was observed. The macula and the optic disk appeared to be torn upward into a 1:30 o'clock position. In January 1989 (at the age of 20 months), photography showed an epibulbar mass in the upper temporal quadrant, an intraocular mass, and an axial distortion of the globe into the 1 to 2 o'clock meridian. At the 5 o'clock position, a depigmentation of the fundus resembling a pavingstone degeneration or a small choroidal coloboma was observed. After anesthesia was achieved, the eye was enucleated and a cystic episcleral mass that reached back to the optic nerve was seen during the operation (Figs. 1 and 2).

Routine serologic tests for cytomegalovirus, rubella, toxoplasmosis, and treponemiasis were all negative. Both orbits were normal in size and shape as determined by computed tomography and conventional radiography. No chromosomal abnormality could be demonstrated.

Pathologic examination—On macroscopic examination the formalin-fixed left eye (measuring 20.5 × 20.5 × 26.5 mm) had sclerectasia resembling staphyloma (Fig. 2) in the left upper quadrant from 4.5 mm behind the corneoscleral limbus as far back as 3 mm from the optic nerve. The sclerectasia measured 13 mm in diameter and about 10 mm in height (prominence). The insertion sites of the six external eye muscles were present with the upper obliquus and the lateral rectus muscle that inserted at the site of the sclerectasia. Brushfield spots were located circumferentially in the iris. The pupil was normal (round) and had no coloboma. Examination of a horizontal section (Fig. 3) disclosed a septate diplophthalmos involving a larger, mature-appearing globe (globe I; 21 mm in length and 16 mm in equatorial diameter) and a smaller, immature-appearing globe (globe II; 18 mm in length and 13 mm in equatorial diameter) that were encapsulated by a common scleral coat in a manner similar to a synophthalmos.

A separating fibrous septum with a triangular connective-tissue core at the periphery was observed. Over a central 8-mm area, the septum was formed by only the uvea and retinae of the two globes. Each eye included a lens, an ora serrata, and a macroscopically unremarkable but opaque retina (fixation artifact) attached posteriorly to what appeared to be an optic disk. The vitreous humor of both globes also appeared unremarkable. One thick and normal optic nerve exited globe I, and a thin connective-tissue appendix was continuous with a posterior retinal attachment site (rudimentary optic disk) on globe II (Figs. 4 and 5). Globe I had a radial yellow-white discoloration of the retinal pigment epithelium and of the underlying uvea in the lower temporal quadrant at the 5 o'clock position. The cornea (horizontal diameter, 11 mm), anterior chamber, trabecular meshwork, iris, ciliary body, and the lens (8 × 3 mm) of globe I appeared normal. Some lighter coloration of the lateral posterior aspect of the anterior connective-tissue septal triangle may have constituted the cornea of globe II (measuring approximately 5 mm). The anterior chamber was not formed in Globe II, the iris seemed to be thinner (possibly hypoplastic), and a large

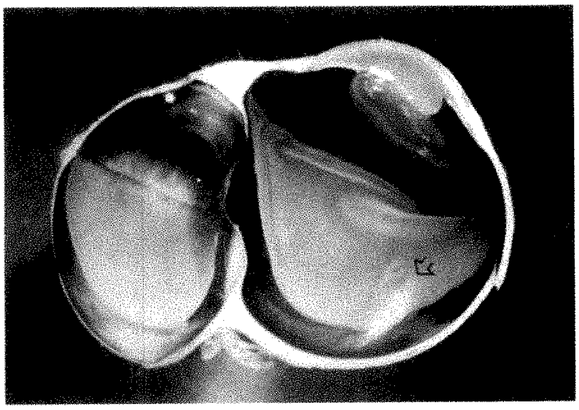

Fig. 3 (Stefani, Hausmann, and Lund). Regular globe I on the right and extra globe II on the left are separated by a fibrous septum. Both globes contain an iris with a pupil, a lens (lens II being smaller than lens I), clear vitreous, a pars plana of the ciliary body, an ora serrata, and a retina. Open arrow marks a localized choroidal coloboma of globe I. The separation of the retina from the retinal pigment epithelium in both eyes is an artifact.

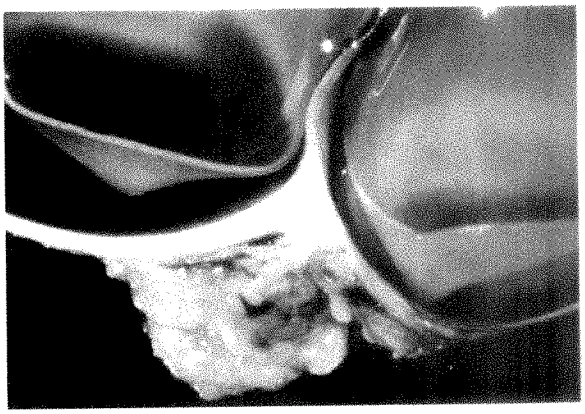

Fig. 4 (Stefani, Hausmann, and Lund). Closer view into the opposite calotte of that shown in Figure 3. The sclera and retina of the extra globe II are thinner than of the normal globe I. Both retinas are fixed to an area resembling a disk at the posterior pole. The separation of the retina from the retinal pigment epithelium in both eyes is an artifact.

pupillary zone was obvious. The umbilicated lens in globe II measured 4.8 × 2 mm. The ciliary processes of globe II were less prominent than those of globe I, whereas the posterior uvea in this globe was less pigmented (except for a round spot at the 6 o'clock position) than that of globe I. Later computed tomography showed a normal chiasm and two apparently normal-appearing optic canals in this child.

Histologic examination—Globe I was almost normal in size and scleral shape except for where it attached to globe II (Fig. 6). The anterior segment structures such as cornea, iris, ciliary body, the lens, and the vitreous body were normal as were the retina, choroid, sclera, optic disk, and optic nerve. Some localized retinal dysplasia was observed in the posterior temporal retina and some Blessig-Iwanoff cysts were seen in the peripheral temporal retina. At the attachment site of globe II, fairly marked retinal pigment epithelium changes and a somewhat less-developed choriocapillaris and choroid were apparent. The retinal pigment epithelium was irregular; some cells were flat,

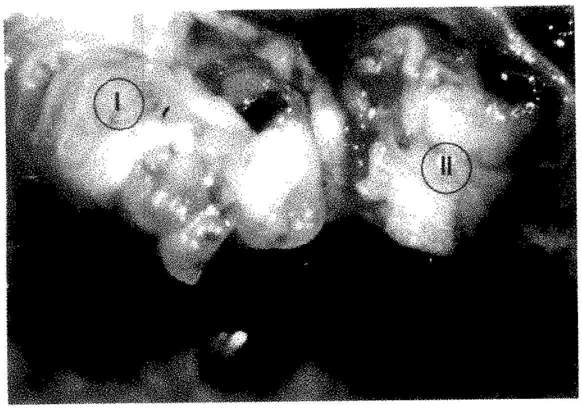

Fig. 5 (Stefani, Hausmann, and Lund). Optic fasciculus area, closer view of Figure 4. I indicates optic fascicle of globe I, II indicates fibrovascular strand, which appeared as optic fasciculus.

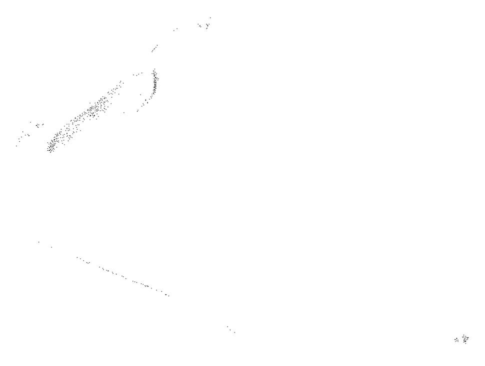

Fig. 6 (Stefani, Hausmann, and Lund). Histologic section of the calotte from Figure 4. Globe I on the left and the supernumerary globe II on the right. The sclera and retina of the extra globe II are thinner than those of the normal globe I. No disk is observed in globe II but a conglomerate of blood vessels is apparent. The separation of the retina from the retinal pigment epithelium in both eyes is an artifact (hematoxylin and eosin stain, × 3.4).

others enlarged, and the retinal pigment epithelium was covered to some extent by a highly cellular layer of nonpigmented retinal pigment epithelium cells. In some places, mineralized deposits resembling drusen were seen between basal retinal pigment epithelium cells. A few ganglion cells were observed in the ciliary nerves adjacent to the optic nerve.

Globe II had a small, flat, pear-shaped configuration, and showed a regular but thinner sclera (0.3 mm) than did globe I (0.4 mm). The scleral bundles were less densely packed in the center of the septal triangles. The retina was also thinner in globe II (0.1 mm) than it was in globe I (0.14 mm). The corneal and angle structures and the anterior chamber were not present. The lens was smaller than normal, its capsule was intact, the densely packed epithelium appeared normal, and the lens fibers showed vacuolation and swelling at the lens equator and at the posterior lens. Many zonules of normal shape were attached to the small lens and to the hypoplastic ciliary body, which was covered by the two-layered epithelium of nonpigmented and pigmented cells. Some epithelial cysts lined by pigmented cells were also seen. A ciliary muscle seemed to be present. The choroid was present but hypoplastic. The vitreous humor was morphologically normal and numerically and cytologically normal hyalocytes were observed. The thin retina was avascular and consisted of normal outer layers and an aplastic inner layer. The photoreceptors with the outer nuclear layer were present in normal location, number, and shape, but the inner nuclear layer was markedly thinned to an average of three nuclear diameters. The inner plexiform layer was present whereas the ganglion cell layer, as well as the nerve-fiber layer, were missing. Some cells with somewhat larger nuclei were located mainly at the inner aspect of the inner plexiform layer. The inner retinal layer was formed by radial glial Müller cells.

Toward the center, retinal layers were irregular because of some cell loss in the inner nuclear layer, cyst formation, focal glial proliferation in the inner retinal layers, and some preretinal tufts. The retinal pigment epithelium cells were thinner than they were in globe I and contained less apical pigment. At the rudimentary optic disk (papilla nervi optici primitiva) the retinal pigment epithelium was flattened with loss of pigment and the formation of a ringlike structure. The retina at the rudimentary optic disk had degenerative changes and a glial proliferation that was in contact with the surface of a loose tissue resembling choroid that contained large tortuous venous blood vessels. At the margin of the retinal contact zone, a strand of tissue covered by retinal pigment epithelium cells was folded down into the rudimentary optic disk. At this level the sclera had an unusual gap large enough to fit an optic fasciculus. The sclera underneath was markedly thin (only a few lamellae in thickness) and was situated over an area of accumulated large arterial/venous blood vessels, and large myelinated nerves. No hints of an optic fasciculus or remnants of it were apparent. An adjacent intrascleral nerve was degenerated and had loss of axons and eosinophilic globule formation.

Discussion

Conditions such as cyclopia with a median single eye or two fused eyes are usually associated with gross deformities of the skull. Olfactory lobes and the entire neuronasal apparatus are usually absent. Supernumerary eye formation in humans is uncommon. In children with two normal orbits it may develop as unilateral synophthalmos or cyclopia with two optic nerves with lateral proboscis. This child did not have a lateral proboscis and her condition seemed to differ from unilateral synophthalmos. The fusion of a fully developed eye and a partly developed eye derived from an eye anlage within one of the two normal orbits is unusual. We termed this abnormality unilateral synophthalmos.

This unilateral malformation with two ectodermal lenses[1] ("no eye contains both surface and neural lens") must have developed in early organogenesis. Previous embryologic and experimental findings have been reviewed. Doubled eyes with doubling of the lenses was almost regularly formed experimentally by Cotronei[2] and Perri[3] on the basis of observations of Rabl[4] and Seefelder.[5]

We concluded that a single primary optic vesicle was formed (globe I with an optic fasciculus), and some unknown damage or depressor[1] occurred when this single primary optic vesicle formed a retinal fold, thus became septated, and induced the double lens formation by contacting the ectoderm. The additional abnormalities such as porencephaly, supernumerary teeth, and branchial cyst may be regarded a result of gross growth disturbance.

The combination of cerebral and ocular malformations in this patient makes an atypical ectodermal anlage more likely than a secondary reaction to an external or internal tissue-damaging effect. Although the major abnormalities occurred in globe II, globe I also had a small area of retinal dysplasia.

Globe II must have been smaller at birth even though increasing internal pressure caused it to enlarge clinically into a fairly well-formed ectatic rudimentary globe. This malformation had some similarities to the cystic coloboma with inverse retina studied and described by von Szily[6] in developing rabbits. Complete aplasia of the optic nerve was found to be associated with a total absence of the retinal vessels and of the optic disk.[7-11] Interestingly enough, globe II of our study contained not only a lens with zonules, but also a retina with photoreceptors and retinal pigment epithelium on its outer aspect and a normal tertiary vitreous humor. The retina was completely avascular and lacked the inner layers and a fully developed optic disk as well as an optic nerve. Our case had some similarities to cases of bilateral optic-nerve aplasia described by Barry[10] and Küchle and associates.[11] Macroscopically, it could be considered a highly differentiated orbital cyst, but microscopically the normal configuration of an outer retina, ciliary body, lens, and choroid in globe II along with a normal disk formation in globe I make this a rather unlikely cause. The formation of a rudimentary optic disk (papilla nervi optici primitiva) in the absence of retinal ganglion cells and the retinal nerve fiber layer is remarkable. Von Szily[6] regarded this disk formation as a major force in retinal development.

The condition in our study might have been caused by an early tissue damage of obscure cause. Hypoplasia or aplasia of the hyaloid blood vessel system in globe II seemed unlikely, but the hyaloid blood vessel system might have been abnormal in both the anterior and the posterior segment of this globe. The hyaloid blood vessel system has an influence on the embryonal development of the lens, the zonules, and the tertiary vitreous humor. Their development in globe II seemed speculative. In this case the anterior hyaloid blood vessel system may have been supplied by ciliary arteries. The fixation of the posterior retina at a rudimentary optic disk (papilla nervi optici primitiva) and the preretinal tufts may indicate the possibility of a regressed abnormal posterior hyaloid artery system that might have been fed by the large retroscleral blood vessels. Additionally, episcleral ciliary nerves were apparent underneath this primitive disk region.

The explosion of a nuclear plant at Chernobyl, U.S.S.R., in the spring of 1986 is another speculative factor that should be mentioned in relation to this abnormality. The conception and early embryonal life of this child had taken place during a period of increased radiation exposure. On the basis of data from the University of Graz, the frequency of monosomy XO (Turner syndrome) increased from four to 12, the frequency of trisomy +18 increased from seven to 15, and the number of remaining aneuploidies increased between April 30, 1986, and Aug. 31, 1987, as compared to the time period of 1985 to 1986, according to the Bureau of the Chancellor of the Republic of Austria.[12] No comprehensive data are available for Germany. Recent data from Finland[13] are regarded as comprehensive. The overall radiation risk is considered to be small.[14,15] Nevertheless, one hit of radiation would be enough to cause damage. Krenn and associates[16] measured radioactive cesium nucleotides in human follicular fluid. Before and shortly after the Chernobyl accident, the results were negative, but became positive in 56% of the tested subjects within the second half year after the nuclear plant explosion. The rate of positive seminal plasma increased accordingly. All the females who tested positive were infertile.

References

1. Mann, I.: Developmental Abnormalities of the Eye, ed. 2. London, British Medical Association, 1957, pp. 30–31.

2. Cotronei, G.: Correlations et differentiations. Arch. Ital. Biol. 71:1, 1921.

3. Perri, T.: Riserche sperimentali sulle doppie formazioni oculari proveniente da unico abbozzo. Arch. Ital. Anat. Embriol. 37:164, 1937.

4. Rabl, C.: Ueber die bilaterale oder nasoseptale Symmetrie des Wirbeltierauges. Arch. Mikroskop. Anat. 75:157, 1917.

5. Seefelder, R.: Comment on T. Perri's paper 1937. Riserche sperimentali sulle doppie formazioni oculari proveniente da unico abbozzo. Zentralbl. Augenheilkd. 38:496, 1937.

6. von Szily, A.: Die Ontogenese der idiotypischen (erblichen) Spaltbildung des Auges, des Mikrophthalmus und der Orbitazysten. Z. Gesamte Anat. I. Abt. 74:1, 1924.

7. Scheie, H. G., and Adler, F. H.: Aplasia of the optic nerve. Arch. Ophthalmol. 26:61, 1941.

8. Edwards, W. C., and Layden, W. E.: Optic nerve hypoplasia. Am. J. Ophthalmol. 70:950, 1970.

9. Acers, T. E.: Congenital Abnormalities of the Optic Nerve and Related Forebrain. Philadelphia, Lea & Febiger, 1983, p. 34.

10. Barry, D. R.: Aplasia of the optic nerves. Int. Ophthalmol. 7:235, 1985.

11. Küchle, M., Kraus, J., Rummelt, C., and Naumann, G. O. H.: Synophthalmia and holoprosencephaly in chromosome 18p deletion defect. Arch. Ophthalmol. 109:136, 1991.

12. Stimpfl, W., and Rosenkranz, W.: Aberrationen im Zeitraum 1980/04/30 bis 1988/05/31. In Bundeskanzleramt Republik Osterreich, Sekt. 7 (ed.): Die Auswirkungen des Reaktorunfalls in Tschernobyl auf Osterreich. Vienna, Austria, Austrian Republic Press, 1988, pp. 252–264.

13. Harjulehto, T., Aro, T., Rita, H., Rytörmaa, T., and Saxen, L.: The accident at Chernobyl and outcome of pregnancy in Finland. Br. Med. J. 298:995, 1989.

14. Källen, B.: Pregnancy outcome in Sweden after Chernobyl. Study with central health registries. Report No. 33621-348/88. Stockholm, National Board of Health and Welfare of Sweden, 1987, p. 1.

15. Czeizel, E., and Billege, B. A.: Csernobili atomerömu-baleset teratologiai ertekelese. Orv. Hetil. 129:457, 1988.

16. Krenn, C. C., Herczeg, K., Feichtinger, W., Albrecht, A., Koppensteiner, E., Mikokit, B., Rahmani, A., Stranzinger, J., Weixelberger, A., Wieser, S., and Unfried, E.: Radioaktives Caesium 137 und Caesium 134 in der Follikel- und Samenflüssigkeit. Geburtshilfe Frauenheilkd. 50:394, 1990.

OPHTHALMIC MINIATURE

From the Sukh Mahal to the Palace the road ran through the heart of the city, and by reason of the continual shouting of the munshis, not more than ten thousand of the fifty thousand people of Boondi knew for what purpose the Sahib was journeying through their midst. Cataract was the most prevalent affliction, cataract in its worst forms, and it was, therefore, necessary that men should come very close to look at the stranger. They were in no sense rude, but they stared devoutly.

Rudyard Kipling, *Letters of Marque*
Allahabad, A. H. Wheeler & Co., 1891, p. 130

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PERSPECTIVES

Collagen Shields

Bartly J. Mondino, M.D.

Collagen shields have been used to promote corneal epithelial healing and to deliver drugs. The collagen shield is shaped like a contact lens and is packaged in a dehydrated form that requires rehydration before application. Because the shield conforms to the shape of the cornea, multiple base curves are not needed. The oxygen permeability of a collagen shield is comparable to a hydroxyethyl-methacrylate lens of similar water content.[1,2] The Bio-Cor collagen shield (Bausch & Lomb, Rochester, New York) and the Collagen Shield and Medilens (Chiron, Irvine, California) are currently available for clinical use. The Bio-Cor collagen shield is made of porcine scleral collagen. Ultraviolet irradiation during manufacture induces variations in collagen cross-linking that produce shields lasting 12, 24, or 72 hours on the eye. The lens has a diameter of approximately 14.5 mm, a base curve of 9 mm, a water content of approximately 65.7%, and a thickness of 0.15 to 0.19 mm centrally.

The Collagen Shield and the newer Medilens are both manufactured from bovine corium collagen and last approximately 24 hours on the eye. The Collagen Shield has a diameter of 14 mm, a base curve of 9.1 mm, and a water content of 80%, whereas the Medilens has a diameter of 16 mm, a base curve of 8.8 mm, and a water content of 83%.

Corneal Epithelial Healing

The mechanical properties of the shield protect the healing corneal epithelium from the blinking action of the eyelids. Additionally, the collagen in the lens may have a beneficial effect on the healing process itself. Shields lasting up to 72 hours may provide a more convenient method of corneal protection than repeated patching. However, collagen shields are not suitable for treating chronic ocular surface disease because they last only a few days. Therefore, the collagen shield will not replace bandage soft contact lenses for chronic diseases because frequent replacement would be inconvenient for the physician and insertion would be difficult for the patient if the lenses were dispensed. The lenses are floppy when hydrated, and a drop of anesthetic is frequently required before insertion. To a large extent, improvements in the quality of collagen shields have eliminated patient complaints of discomfort associated with their use.

The effect of collagen shields on epithelial healing has been evaluated in animal studies. In rabbit eyes with central superficial keratectomies, the rate of corneal epithelialization was increased in eyes treated with the collagen shield.[3] Another study examined the effect of collagen shields on rabbit corneas with central epithelial defects from chemical injury.[4] Although no adverse effects attributable to the shield were observed, accelerated epithelialization in the shield-treated group was not demonstrated. In a study of mechanically de-epithelialized cat corneas, treatment with collagen shields did not increase the rate of epithelial growth.[5] However, untreated defects increased in size during the first eight hours of the experiment. Radial keratotomies were performed in rabbits in two studies.[6,7] Compared to an untreated control group, histopathologic examination of corneas treated with shields demonstrated more complete epithelial healing, as indicated by surface microvilli and differentiation into multiple layers[7] and less inflammation and edema.[6,7]

Collagen shields have also been evaluated in human wound-healing studies. In a study of penetrating keratoplasty, improved epithelial healing was observed on the first and eighth postoperative days in eyes treated with collagen shields, although the difference at eight days was not statistically significant.[8] A thick collagenous film over the entire ocular surface was observed on the first postoperative day after keratoplasty and cataract surgery.[9] After radial keratotomy, the shield-treated group demonstrated faster resolution of corneal inflammation and edema, greater decrease in myopia, and less fluctuation in the refraction at six months.[6] Additionally, collagen shields were used to promote healing of leaking glaucoma filtering blebs.[10,11]

Drug Delivery

Drug delivery by collagen shields has advantages over other modes of drug delivery; frequent topical application can be labor-intensive and irritating, and subconjunctival injections can be painful and dangerous for the patient and inconvenient for the physician. Collagen shields have been used to treat infectious corneal ulcers and to prevent postoperative infections.[9,12]

Drug delivery by collagen shields depends on absorption and subsequent release of the drug by the shield. When a shield is rehydrated in a solution containing a water-soluble drug, the drug becomes trapped in the collagen matrix. Additionally, some drugs may undergo reversible binding to collagen.[13] The drug is released as the shield dissolves on the eye. Shields soaked in water-soluble drugs produced corneal and aqueous levels comparable to frequent topical therapy.[14] Collagen shields can also be used to deliver the water-insoluble drug, cyclosporine, but this agent has to be incorporated into the shield at the time of manufacture.[15]

Collagen shields have been used to deliver gentamicin, vancomycin, tobramycin, dexamethasone, prednisolone, amphotericin B, cyclosporine, and heparin.[15-23] In all these studies, drug delivery by collagen shields has been found to be comparable or superior to eyedrop therapy or subconjunctival injection. Collagen shields have also been used to treat animal models of disease. Collagen shields delivering cyclosporine were found to be superior to cyclosporine eyedrops in the prevention and treatment of corneal-graft rejection in a high-risk keratoplasty model.[22] Collagen shields impregnated with tobramycin were found to have a comparable antimicrobial effect in one study[16] and a superior effect in another study[23] when compared to tobramycin eyedrops in a rabbit model of keratitis caused by *Pseudomonas* sp. Laboratory studies have suggested that collagen shields may support microbial growth and adherence, but the clinical implications of these findings in the induction or treatment of infectious keratitis are not known.[24]

Collagen shields can be used to deliver combinations of drugs. Two antibiotics are commonly used in the initial treatment of corneal ulcers to provide broad-spectrum coverage. Combining gentamicin and vancomycin in a collagen shield did not decrease delivery of either drug when compared to delivery of each drug separately.[13] Conversely, combining gentamicin and cefazolin in solution resulted in precipitation, precluding incorporation of this particular drug combination into a collagen shield.[13] Only drugs that are compatible pharmacologically should be incorporated into collagen shields. For example, the combination of an aminoglycoside such as gentamicin and a penicillin such as mezlocillin should be avoided because of inactivation of the aminoglycoside by the penicillin.[25] Of greater concern, a recent clinical alert by the American Academy of Ophthalmology (Clinical Alert 11/1, AAO, November 9, 1990) concerned patients who developed corneal epithelial loss and edema after the application of a collagen shield previously impregnated with both Solu-Medrol (40 mg/ml of methylprednisolone sodium succinate for injection) and gentamicin sulfate (40 mg/ml of gentamicin sulfate injection). Mixing of the two drugs produced an aggregate, but it was unclear whether the aggregate damaged the cornea by causing chemical toxicity or by mechanical abrasion. Care should be exercised when drugs are combined for delivery by collagen shields to make sure that the drug combination does not result in precipitates.

Collagen shields have been used to deliver drugs after anterior segment surgery to avoid subconjunctival injections, which can be painful even after an adequate retrobulbar anesthetic injection.[26] If subconjunctival injections are to be replaced by collagen shields, a compatible combination of corticosteroid and antibiotic must be used. Also, the additional cost of collagen shields should be considered when they are used for postoperative drug delivery.

Collagen shields have been used to promote corneal epithelial healing and to deliver drugs. Collagen shields deliver many drugs to animal eyes as well as or better than frequent eyedrop therapy or subconjunctival injection. Drug delivery by collagen shields was effective in the treatment of animal models of graft rejection and bacterial keratitis.

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References

1. Weissman, B. A., and Lee, D. A.: Oxygen transmissibility, thickness, and water content of three types of collagen shields. Arch. Ophthalmol. 106:1706, 1988.

2. Weissman, B. A., Brennan, N. A., Lee, D. A., and Fatt, I.: Oxygen permeability of collagen shields. Invest. Ophthalmol. Vis. Sci. 31:334, 1990.

3. Frantz, J. M., Dupuy, B. M., Kaufman, H. E., and Beuerman, R. W.: The effect of collagen shields on epithelial wound healing in rabbits. Am. J. Ophthalmol. 108:524, 1989.

4. Robin, J. B., Keys, C. L., Kaminiski, L. A., and Viana, M. A. G.: The effect of collagen shields on rabbit corneal reepithelialization after chemical debridement. Invest. Ophthalmol. Vis. Sci. 31:1294, 1990.

5. Shaker, G. J., Ueda, S., LoCascio, J. A., and Aquavella, J. V.: Effect of a collagen shield on cat corneal epithelial wound healing. Invest. Ophthalmol. Vis. Sci. 30:1565, 1989.

6. Marmer, R. H.: Therapeutic and protective properties of the corneal collagen shield. J. Cataract Refract. Surg. 14:496, 1988.

7. Aquavella, J. V., del Cerro, M., Musco, P. S., and Ueda, S.: The effect of a collagen bandage lens on corneal wound healing. A preliminary report. Ophthalmic Surg. 18:570, 1987.

8. Ruffini, J. J., Aquavella, J. V., and LoCascio, J. A.: Effect of collagen shields on corneal epithelialization following penetrating keratoplasty. Ophthalmic Surg. 20:21, 1989.

9. Aquavella, J. V., Ruffini, J. J., and LoCascio, J. A.: Use of collagen shields as a surgical adjunct. J. Cataract Refract. Surg. 14:492, 1988.

10. Fourman, S., and Wiley, L.: Use of a collagen shield to treat a glaucoma filter bleb leak. Am. J. Ophthalmol. 107:673, 1989.

11. Weber, P. A., and Baker, N. D.: The use of cyanoacrylate adhesive with a collagen shield in leaking filtering blebs. Ophthalmic Surg. 20:284, 1989.

12. Pollard, D. E., and Kaufman, H. E.: Clinical uses of collagen shields. J. Cataract Refract. Surg. 14:489, 1988.

13. Phinney, R. B., Schwartz, S. D., Lee, D. A., and Mondino, B. J.: Collagen-shield delivery of gentamicin and vancomycin. Arch. Ophthalmol. 106:1599, 1988.

14. Hwang, D. G., Stern, W. H., Hwang, P. H., and MacGowan-Smith, L. A.: Collagen shield enhancement of topical dexamethasone penetration. Arch. Ophthalmol. 107:1375, 1989.

15. Reidy, J. J., Gebhardt, B. M., and Kaufman, H. E.: The collagen shield. A new vehicle for delivery of cyclosporine A to the eye. Cornea 9:196, 1990.

16. Hobden, J. A., Reidy, J. J., O'Callaghan, R. J., Hill, J. M., Insler, M. S., and Rootman, D. S.: Treatment of experimental Pseudomonas keratitis using collagen shields containing tobramycin. Arch. Ophthalmol. 106:1605, 1988.

17. Unterman, S. R., Rootman, D. S., Hill, J. M., Parelman, J. J., Thompson, H. W., and Kaufman, H. E.: Collagen shield drug delivery. Therapeutic concentrations of tobramycin in the rabbit cornea and aqueous humor. J. Cataract Refract. Surg. 14:500, 1988.

18. O'Brien, T. P., Sawusch, M. R., Dick, J. D., Hamburg, T. R., and Gottsch, J. D.: Use of collagen corneal shields versus soft contact lenses to enhance

penetration of topical tobramycin. J. Cataract Refract. Surg. 14:505, 1988.

19. Schwartz, S. D., Harrison, S. A., Engstrom, R. E., Bawdon, R. E., Lee, D. A., and Mondino, B. J.: Collagen shield delivery of amphotericin B. Am. J. Ophthalmol. 109:701, 1990.

20. Sawusch, M. R., O'Brien, T. P., and Updegraff, S. A.: Collagen corneal shields enhance penetration of topical prednisolone acetate. J. Cataract Refract. Surg. 15:625, 1989.

21. Murray, T. G., Stern, W. H., Chin, D. H., and MacGowan-Smith, L. A.: Collagen shield heparin delivery for prevention of postoperative fibrin. Arch. Ophthalmol. 108:104, 1990.

22. Chen, Y. F., Gebhardt, B. M., Reidy, J. J., and Kaufman, H. E.: Cyclosporine-containing collagen shields suppress corneal allograft rejection. Am. J. Ophthalmol. 109:132, 1990.

23. Sawusch, M. R., O'Brien, T. P., Dick, J. D., and Gottsch, J. D.: Use of collagen corneal shields in the treatment of bacterial keratitis. Am. J. Ophthalmol. 106:279, 1988.

24. Asbell, P. A., Namdari, H., and Hartman, E. J.: Microbial adhesion and growth on collagen shields. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 1166.

25. Sande, M. A., and Mandell, G. L.: Antimicrobial agents. In Gilman, A. G., Goodman, L. S., Rall, T. W., and Murad, F. (eds.): Goodman and Gilman's Pharmacological Basis of Therapeutics, ed. 7. New York, Macmillan Publishing Company, 1985, pp. 1154–1192.

26. Friedberg, M. L., Pleyer, U., Mondino, B. J.: Device drug delivery to the eye. Collagen shields, iontophoresis, and pumps. Ophthalmology 98:725, 1991.

Residual Intrascleral and Intraretinal Melanoma: A Concern With Lamellar Sclerouvectomy for Uveal Melanoma

Dennis M. Robertson, M.D., R. Jean Campbell, M.D., and Daniel T. Weaver, M.D.

Surgical resection of uveal melanomas has been advocated in selected cases as an alternative to radiation therapy or enucleation.[1-6] In addition to full-thickness eye-wall resection, sclerouvectomy under a lamellar scleral flap, with or without preservation of the retina, has been described. In general, the numbers of patients so treated are small, the follow-up is short, and statements concerning the incidence of metastases and patient survival are speculative at best. Meaningful statistics regarding the potential benefits or disadvantages associated with any treatment for melanoma require large numbers of patients and long follow-up. For example, the Collaborative Ocular Melanoma Study has estimated that to demonstrate a 25% difference in five-year mortality between enucleation and radiation with ^{125}I-brachytherapy, more than 1,000 patients must be enrolled and randomized between the two treatment groups for the results to achieve statistical validity with a power of 80% or more.[7] Accordingly, with a new or seldom used procedure, it is not possible to conclude fairly that the procedure enhances or worsens patient survival. On the same basis, it cannot be concluded that the procedure does not worsen patient survival. In surgical oncology the ultimate test of a procedure is patient survival or death from metastasis. For uveal melanoma, follow-up well beyond five years may be necessary before differences in treatment become manifest as differences in survival.

Since it is unrealistic to consider the efficacy of infrequently used treatments as lifesaving procedures, it is important to consider the nature of the treatments themselves. In particular, it is important to acknowledge the local ocular complications, to recognize the potential problems, and then determine if the type and frequency of these problems are acceptable.

Lamellar sclerouvectomy involves making a scleral incision to a depth of 80% of its thickness to create a lamellar flap which is hinged posteriorly. The underlying tumor and sclera are removed and the hinged flap of sclera is sutured back into position. Whether a melanoma is surgically excised with sclerouvectomy or full-thickness eye-wall resection, operative and postoperative complications may result in the need for subsequent enucleation. Peyman and colleagues[3] reported that 11 of 34 eyes treated with eye-wall resection required enucleation, six because of operative or postoperative complications. Among a series of 26 eyes with relatively large ciliary body and ciliochoroidal melanomas treated with lamellar sclerouvectomy between 1983 and 1989, D. H. Char, J. R. Castro, T. L. Phillips, S. N. Knoll, and J. N. Quwey observed that eight eyes required enucleation (oral communication, March 1991, and written communication, August 1991). Perhaps more importantly, available information demonstrates histopathologic evidence of tumor cells at the margin of resection in a large percentage of cases. Kara,[1] reporting on 15 years of experience in excising uveal melanomas, cautioned that "despite the intensive preoperative study of these tumors, the surgeon does not know with absolute certainty the extent of the surgical procedure that will eventually be necessary." In seven of 11 enucleated eyes reported by Peyman and colleagues,[3] there was histopathologic evidence of tumor cells at the margin of resection. Forrest, Keyser, and Spencer[8] reported that in 68 of 107 cases tumor cells were present at the edge of the resection. Thirteen of the 26 eyes treated by Char and associates had histopathologic evidence of tumor cells at the resected margin even when a 2- to 3-mm boundary of normal-appearing uvea was included in the resection. Although it is possible that fixation artifacts could make it appear falsely that the choroidal edge of resection is involved by tumor cells, the presence of malignant cells at the resected margin suggests that malignant cells are left behind. Certainly, this was true in some cases, as three of the 13 eyes developed local recurrences during follow-up.

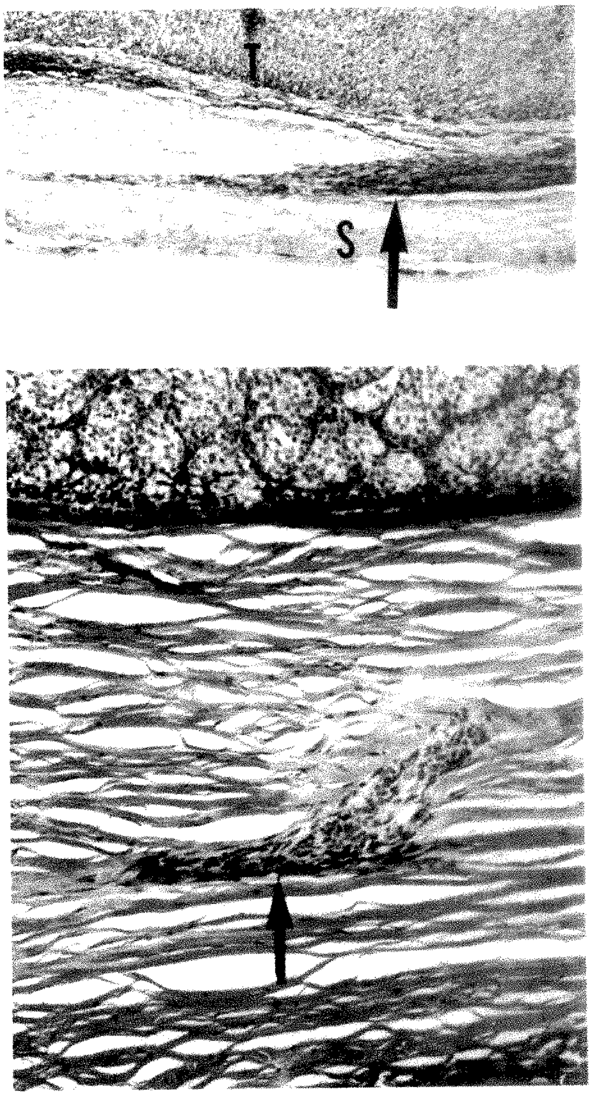

Fig. 1 (Robertson, Campbell, and Weaver). Photomicrographs of eyes containing mixed-cell choroidal melanomas that have invaded the sclera via the emissary channels (arrows). Tumor cells would be included in the flap of a lamellar dissection prepared to a depth of 80% of the scleral thickness (top, hematoxylin and eosin, × 63; bottom, hematoxylin and eosin, × 160). T indicates main tumor; S, sclera.

Another concern with lamellar sclerouvectomy for uveal melanoma relates to the presence of tumor cells in the sclera overlying the tumor. From our pathology laboratory, we reviewed 30 consecutive uveal enucleations for previously untreated malignant uveal melanoma. The sections studied were 8 μm thick and approximately 16 μm or more apart; eight randomized step-sections were cut from each paraffin block. Eight of the 30 eyes (27%) had tumor cells in the outer 80% of the sclera (Fig. 1). In seven of these eight eyes, tumor cells were found in the outer 60% of the sclera. These findings of scleral invasion were seen in both posteriorly and anteriorly located melanomas. The finding of intrascleral invasion of choroidal melanoma was also reported by Donders.[9] He observed intrascleral invasion with melanoma cells in 30% of eyes studied with nonserial sections. This increased to 80% when studied with serial sections. In view of the high frequency of scleral tumor invasion, the extent of which cannot be judged clinically, Naumann, Volker, and Gackle[2] argued that any attempts at surgical removal should always include the entire overlying sclera.

A fundamental axiom in the surgical treatment of cancer is complete tumor excision. In a significant number of eyes undergoing sclerouvectomy for choroidal melanoma, histologic evidence of tumor cells at the margins of resection and the frequent finding of cells in the sclera overlying the tumor indicate that a complete resection with this technique cannot be accomplished with confidence. When melanoma cells are left behind, the surgical approach has obviously not achieved the traditional goal of totally removing the malignancy. Incomplete tumor removal may be acceptable as a palliative treatment when better alternatives are not available, but the incomplete removal of an intraocular melanoma may not be acceptable. It can be argued that adjunctive treatment, such as postoperative radiation, cryotherapy, or photocoagulation, after local resection should be used, but this approach only acknowledges that the surgical resection of a melanoma is an uncertain technique for the total removal of an intraocular melanoma.

In addition to the scleral invasion by melanoma cells observed in eight of the 30 eyes enucleated for choroidal melanomas, malignant melanoma cells locally invaded the retina in seven of the 30 eyes studied (Fig. 2).

Intraretinal invasion by melanoma cells may be recognized clinically in some cases, but it cannot be clinically recognized with certainty in all cases. This information should be a concern among those surgeons who perform a lamellar dissection over a melanoma and remove the tumor while attempting to preserve the overlying retina. In addition to leaving tumor cells in the scleral flap, in approximately one fourth of the cases malignant melanoma cells likely remain in the retina in approximately one fifth of the cases.

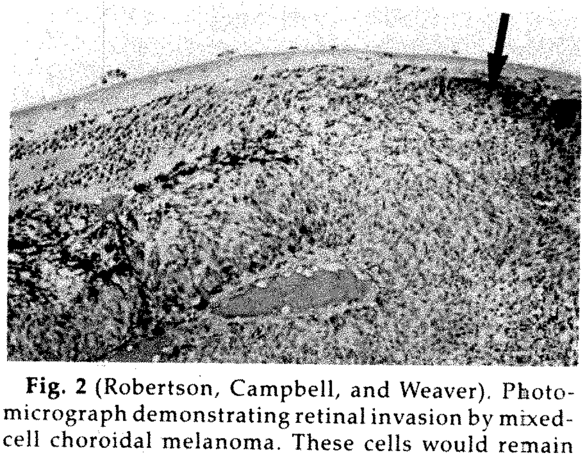

Fig. 2 (Robertson, Campbell, and Weaver). Photomicrograph demonstrating retinal invasion by mixed-cell choroidal melanoma. These cells would remain in situ following a retina-sparing lamellar sclerouvectomy (hematoxylin and eosin, × 160).

What do these findings truly mean? What is the significance of leaving nests of malignant cells in the retained retina, at the edge of the choroidal resection, or in the scleral flap over the resection? How realistic is it to conclude that these cells will not grow? Early follow-up reports suggest that the frequency of local tumor recurrence in eyes having undergone surgical resection of a malignant melanoma is low. Foulds and Damato[5] described 157 patients treated with retina-sparing lamellar sclerouvectomy and commented on the difficulties in recognizing residual tumor or local recurrence. They did not report the number of eyes that showed residual tumor or had recurrences but they did report a 79% five-year survival among the 33 patients followed up as long as five years. Forrest, Keyser, and Spencer[8] concluded that, although complete excision had been accomplished in only one third of the cases they reviewed, intraocular recurrence of the tumor occurred in the first four years of follow-up in only approximately one fifth of the remaining cases. The high percentage of eyes treated with lamellar sclerouvectomy in which histopathologic study demonstrates tumor cells at the line of resection or in the sclera overlying the tumor generates concern that there will be an increased frequency of local recurrence as well as distant metastases with longer follow-up. Answers to some of these questions and concerns may be learned with continued careful observation and data analysis. Meanwhile, it seems fitting to conclude with a summary sentence published in 1989 by Foulds and Damato,[5] "Local surgical resection in common with all other so-called conservative methods of treatment of choroidal melanoma must be regarded as experimental and an unproven form of management."

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References

1. Kara, G. B.: Excision of uveal melanomas. A 15-year experience. Ophthalmology 86:997, 1979.
2. Naumann, G. O. H., Volker, H. E., and Gackle, D.: The block excision of malignant melanoma of the ciliary body and the peripheral choroid. Doc. Ophthalmol. 50:43, 1980.
3. Peyman, G. A., Juarez, C. P., Diamond, J. G., and Raichand, M.: Ten years' experience with eye wall resection of uveal malignant melanomas. Ophthalmology 91:1720, 1984.
4. Shields, J. A., and Shields, C. L.: Surgical approach to lamellar sclerouvectomy for posterior uveal melanomas. Ophthalmic Surg. 19:774, 1988.
5. Foulds, W. S., and Damato, B. E.: Surgical resection of choroidal melanomas. In Ryan, S. J., and Schachat, A. P. (eds.): Retina, vol. 1., Chap. 46. St. Louis, C. V. Mosby, 1989, pp. 713–720.
6. Augsburger, J. J., Lauritzen, K., Gamel, J. W., DeBrakeleer, D. J., Lowry, J. C., and Eisenman, R.: Matched group study of surgical resection versus cobalt-60 plaque radiotherapy for primary choroidal or ciliary body melanoma. Ophthalmic Surg. 21:682, 1990.
7. Collaborative Ocular Melanoma Study Group: Statistical Considerations, Chapter 20. COMS Manual of Procedures. Springfield, Virginia, National Technical Information Service, 1989, NTIS Accession No. PB90-115536.
8. Forrest, A. W., Keyser, R. B., and Spencer, W. H.: Iridocyclectomy for melanomas of the ciliary body. A follow-up study of pathology and surgical morbidity. Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:1237, 1978.
9. Donders, P. C.: Malignant melanoma of the choroid. Trans. Ophthalmol. Soc. U.K. 93:745, 1973.

LETTERS TO THE JOURNAL

Fatal Mucormycosis Therapy Associated With Deferoxamine

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A 67-year-old man had increasing left periorbital pain and swelling of six days' duration. He had chronic renal failure, which required hemodialysis. Ten years previously a renal transplant had failed in the short-term. No immunosuppressive therapy was required after that time. He had been taking 1 g of deferoxamine three times a week for the treatment of iron and aluminum overload from 1985 to 1987 and for 18 months before the present admission. There were no recent symptoms of nasal or sinus disease.

Examination showed he was alert and afebrile. Best-corrected visual acuity was R.E.: 20/15 and L.E.: 20/30. He had normal pupils and color vision. The left globe was proptosed and inferiorly displaced by a tender mass in the superior orbit. The upper eyelid skin was erythematous but had good capillary return. There was a complete blepharoptosis and grossly restricted elevation of the globe. The fundus was normal.

Computed tomography showed a poorly defined mass in the anterosuperior orbit with mild mucosal thickening of the adjacent frontal and ethmoid sinuses. Blood cultures and conjunctival swabs showed no pathogenic organisms.

A provisional diagnosis of bacterial orbital cellulitis was made and intravenous cefotaxime sodium was initiated. During the next 24 hours, visual acuity deteriorated to 20/60 with a relative afferent pupillary defect. A biopsy specimen was obtained. The skin bled normally, but deep to the orbital septum was a firm mass of gray-yellow orbital fat with dark flecks that did not bleed on biopsy. Immediate Gram stain showed no organisms but histopathologic examination and cultures confirmed mucormycosis.

Amphotericin was instituted intravenously immediately. The orbit was exenterated, and a radical frontoethmoidectomy was performed within several hours of the diagnosis being made. Tissue at the apex of the orbit bled freely and appeared normal. However, fungal hyphae were found in the posterior orbit, and in the frontal and ethmoid sinuses.

Postoperatively, the patient became increasingly confused and computed tomogram disclosed frontal lobe involvement. We elected not to offer any further surgical treatment. He died 37 days after admission. Permission for autopsy was refused.

Several reports of the association between treatment with deferoxamine in renal dialysis patients and the development of rhino-orbito-cerebral mucormycosis have appeared in the medical literature.[1-4] Not all patients have been on hemodialysis.[5] As with our patient, these patients were generally not immunosup-

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pressed. It has been suggested that deferoxamine and iron may act as fungal growth factors.[3]

Patients with orbital cellulitis generally are seen by ophthalmologists. It is vital therefore that we be aware of the association between deferoxamine and mucormycosis. Aggressive investigation and treatment including radical surgery may prevent an otherwise fatal outcome.

References

1. Veis, J. H., Contiguglia, R., Klein, M., Mishell, J., Alfrey, A. C., and Shapiro, J. I.: Mucormycosis in deferoxamine-treated patients on dialysis. Ann. Intern. Med. 107:258, 1987.
2. Windus, D. W., Stokes, J. S., Julian, B. A., and Fenves, A. Z.: Fatal *Rhizopus* infections in hemodialysis patients receiving deferoxamine. Ann. Intern. Med. 107:678, 1987.
3. Goodill, J. J., and Abuelo, J. G.: Mucormycosis. A new risk of deferoxamine therapy in dialysis patients with aluminum or iron overload? N. Engl. J. Med. 317:54, 1987.
4. Johnson, E. V., Kline, L. B., Julian, B. A., and Garcia, J. H.: Bilateral cavernous sinus thrombosis due to mucormycosis. Arch. Ophthalmol. 106:1089, 1988.
5. Rex, J. H., Ginsberg, A. M., Fries, L. F., Pass, H. I., and Kwon-Chung, K. J.: *Cunninghamella bertholletiae* infection associated with deferoxamine therapy. Rev. Infect. Dis. 10:1187, 1988.

Bilateral Nongranulomatous Uveitis and a Poststreptococcal Syndrome

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A previously healthy 24-year-old man complained of a sore throat, coryza, night sweats, and malaise. Mild injection of the oropharynx was noted by his internist and treatment with erythromycin was initiated orally. Two weeks later, he developed cough, wheezing, nonlocalizing abdominal pain, and bilateral ocular pain.

Physical examination disclosed a fever of 101 F. Ophthalmic examination disclosed visual acuity of 20/20 in each eye. Mild bulbar, conjunctival injection was present bilaterally. Fine, white keratic precipitates were present on the corneal endothelium, and a moderate cell and flare reaction was noted in the anterior chambers in both eyes. Cellular precipitates were present on the posterior lens surface, which corresponded to the area of Wieger's hyaloideocapsular ligament (Figure). Intraocular pressure was 10 mm Hg in each eye. Ophthalmoscopy disclosed a mild vitreous cellular reaction and clumps of cells near the inferior vitreous base in both eyes.

Laboratory evaluation disclosed a hematocrit level of 31.7%, Westergren sedimentation rate of 95 mm/hr, increased blood urea nitrogen and creatinine, rare red and white blood cells in the urine, and mild proteinuria. Serum protein electrophoresis, angiotensin-converting enzyme, tuberculin skin test, and assays for toxoplasmosis, histoplasmosis, coccidiomycosis, blastomycosis, and Lyme disease were normal. Rheumatoid factor was slightly reactive at 1:20 and the antinuclear antibody was negative. Antistreptococcal hyaluronidase titer was positive at 1:256, and antistreptococcal DNase B

Figure (Cokingtin and Han). Slit-lamp photograph of the left eye demonstrated cellular precipitates on the posterior lens surface. Precipitates formed ringlike arrangements corresponding to Wieger's hyaloideocapsular ligament in both eyes.

was positive at 1:120. A renal sonogram was normal.

One week later, the patient developed biopsy-proven erythema nodosum on the extensor surfaces of both legs. Subsequent testing showed normal renal function, falling antistreptococcal hyaluronidase and antiDNase titers, and resolution of anemia. Ocular inflammation responded over two months to treatment with topically applied corticosteroids and cycloplegics.

In this case, the findings of pharyngitis, renal insufficiency, anemia, erythema nodosum, and positive antistreptococcal antibody titers strongly support a diagnosis of a poststreptococcal syndrome. As well as known nonsuppurative complications of the poststreptococcal syndrome,[1] this individual also experienced bilateral nongranulomatous uveitis. Although experimental[2,3] and epidemiologic[4] evidence supports a link between bacterial disease and uveitis, we are unaware of any specific reports of uveitis associated with a presumed poststreptococcal syndrome. We suspect the type of uveitis exhibited by this case, albeit rare, may be a distinct entity by virtue of its association with other nonsuppurative poststreptococcal complications, and should be differentiated from other forms of uveitis. As such, the term poststreptococcal uveitis may be an appropriate designation.

References

1. Wilson, J.D., Braunwald, E., Isselbacher, K. J., Petersdorf, R.G., Martin, J. B., Fauci, A. S., and Root, R. K. (eds.): Harrison's Principles of Internal Medicine, ed. 12. New York, McGraw-Hill, Inc., 1991, pp. 1170–1172.

2. Wells, A., Pararajasegaram, G., Baldwin, M., Yang, C., Hammer, C., and Fox, A.: Uveitis and arthritis induced by systemic injection of streptococcal cell walls. Invest. Ophthalmol. Vis. Sci. 27:921, 1986.

3. Fox, A., Hammer, M. E., Lill, P., Burch, T. G., and Burrish, G.: Experimental uveitis elicited by peptidoglycan-polysaccharide complexes, lipopolysaccharide, and muramyl dipeptide. Arch. Ophthalmol. 102:1063, 1984.

4. Wakefield, D., Stahlberg, T. H., Toivanen, A., Granfors, K., and Tennant, C.: Serologic evidence of *Yersinia* infection in patients with anterior uveitis. Arch. Ophthalmol. 108:219, 1990.

Rhodococcus luteus and *Rhodococcus erythropolis* Chronic Endophthalmitis After Lens Implantation

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Insidious chronic endophthalmitis of late onset after lens implantation is a rare complication, caused by a variety of different bacterial and fungal agents.

An 82-year-old immunocompetent woman was seen because of chronic endophthalmitis in her left eye nine months after an uncomplicated extracapsular cataract extraction with implan-

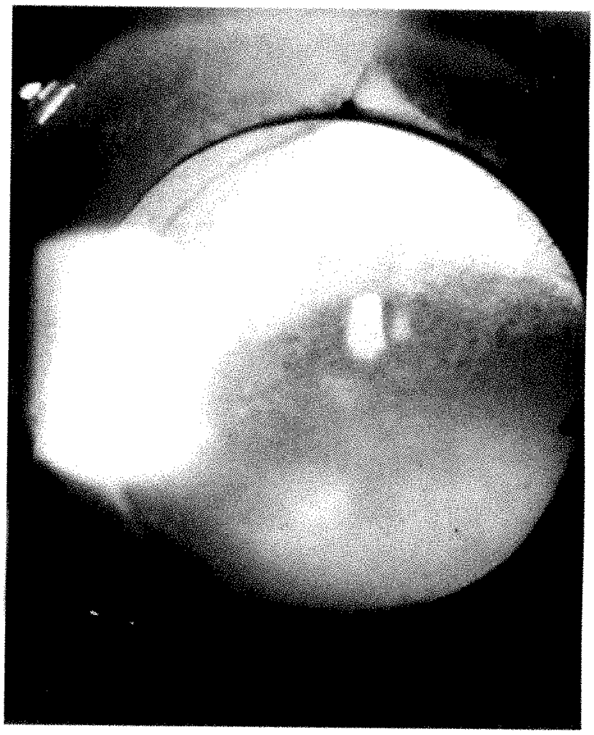

Fig. 1 (von Below and associates). Late-onset, chronic endophthalmitis after lens implantation in the intact posterior capsular sac; in transillumination.

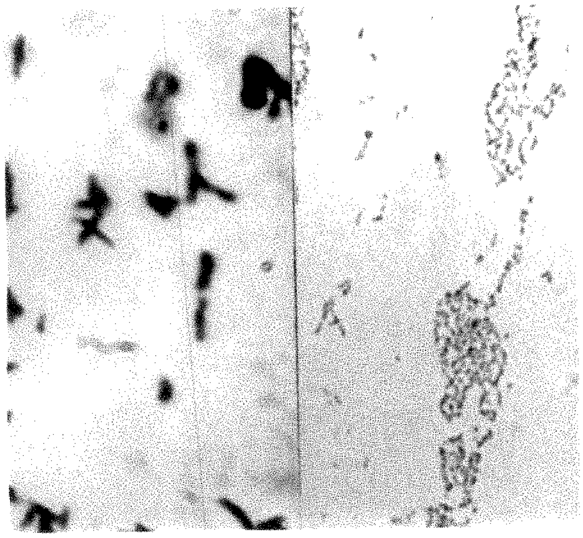

Fig. 2 (von Below and associates). Left, Gram-positive aerobic rods. *R. luteus* with branching filaments (Gram, × 630). Right, Gram-positive aerobic cocci. *R. erythropolis* (Gram, × 380).

tation of a posterior chamber lens. The inflammation was centered around the intact posterior capsular sac (Fig. 1). Results of conjunctival cultures were negative. Antibacterial and antimycotic systemic treatment did not resolve the inflammation. Removal of the intraocular lens with the capsule and anterior vitrectomy cured the endophthalmitis. Postoperative visual acuity was 20/30 with a contact lens and remained stable in the 12-month follow-up period.

Results of light microscopy and culture showed gram-positive bacteria both in intraoperative material and vitreous aspirate. These organisms were identified at the Institute for Medical Microbiology and Immunology in Bonn as a mixed flora of two morphologically related entities: *Rhodococcus erythropolis* and *R. luteus* (Fig. 2). These and other species of the genus *Rhodococcus* are widely distributed in nature and particularly found in soil and feces of herbivores (horses, sheep, and cattle[1,2]). They are closely related to species of the genera *Corynebacterium*, *Mycobacterium*, and *Nocardia*. During multiplication, *Rhodococcus* species undergo a coccus-rod-coccus growth cycle, which may lead to branching filaments. The growth cycle of *R. erythropolis* is completed by the appearance of cocci, whereas *R. luteus* usually forms shorter or longer, straight to slightly curved rods.

Rhodococcus species were described as a cause of a corneal ulcer[4] and as endophthalmitis[3,5] after perforating trauma.

Anterior vitrectomy with removal of the intraocular lens may be necessary, when a systemic regimen of antibiotic and antimycotic treatment (2 g of cefotiam three times a day; 250 mg of amikacin twice a day; and 25 mg of amphotericin B twice a day for ten days) is not effective in resolving the localized endophthalmitis of sensitive and causative agents.

References

1. Jones, M. R., Neale, T. J., and Say, P. J.: *Rhodococcus equi*. An emerging opportunistic pathogen? Austr. N.Z. Med. 19:103, 1989.

2. Richet, H. M., Craven, P. C., Brown, J. M., and Lasker, B. A.: A cluster of *Rhodococcus* (*Gordona*) bronchialis sternal wound infections after coronary artery bypass surgery. N. Engl. J. Med. 324:104, 1991.

3. Ebersole, L. L., and Paturzo, J. L.: Endophthalmitis caused by *Rhodococcus equi* Prescott serotype 4. J. Clin. Microbiol. 26:1221, 1988.

4. Gopaul, D., Ellis, C. Maki, A., Jr., and Joseph, M. G.: Isolation of *Rhodococcus* from a chronic corneal ulcer. Diagn. Microbiol. Infect. Dis. 10:185, 1988.

5. Hillman, D., Garrestson, B., and Fascella, R.: *Rhodococcus equi* endophthalmitis. Arch. Ophthalmol. 107:20, 1989.

Retinal Nerve Fiber Layer Infarct in a Patient With Babesiosis

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Babesiosis is a protozoan infection of the red blood cells. It is prevalent in the coastal areas of southern New England. The disease is transmitted from a rodent reservoir by the deer tick, *Ixodes dammini*, which is also the vector of Lyme disease. Most infections are mild or subclinical although in immunocompromised or asplenic patients a severe, rarely fatal, hemolytic anemia can occur.[1] Ocular abnormalities are

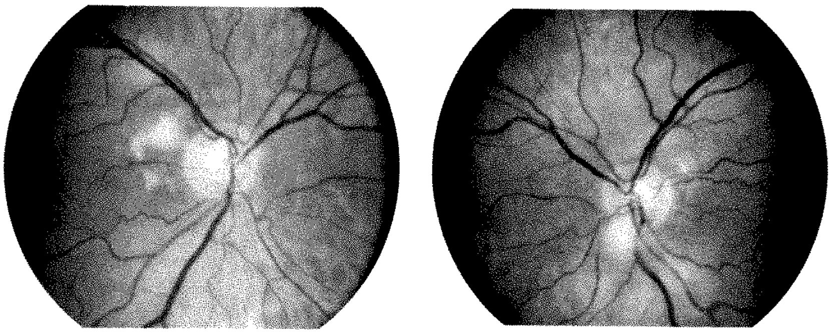

Figure (Zweifach and Shovlin). Left, Right fundus with nerve fiber layer infarct temporal to disk. Right, Left fundus with nerve fiber layer infarct inferior to disk.

not usually considered a feature of this disease. They have been reported in an asplenic patient who had other possible medical problems.[2] We found identical ocular abnormalities in an otherwise healthy man.

The patient, a 52-year-old man, had visited Shelter Island, in Long Island Sound, New York, two months previously. He developed a flu-like illness followed by anemia and fever. The hemoglobin level decreased from 11.0 to 8.8 mg/dl and the hematocrit concentration from 33.0% to 25.1%. Reticulocytes were 5%. Peripheral blood smears showed intraerythrocytic parasites consistent with *Babesia microti*. On the tenth day of illness the patient complained of a scotoma in the field of vision of the right eye. A large nerve fiber layer infarct was found superotemporal to the disk in this eye (Figure, left). A similar lesion was found at the inferior margin of the left disk (Figure, right). Ocular findings were otherwise normal. The patient was stabilized medically and was discharged. At the three-month follow-up the visual complaint persisted and the nerve fiber layer infarct had resolved.

A case of babesiosis with virtually identical nerve fiber layer infarcts was reported by Ortiz and Eagle.[2] They left room for doubt about the specificity of the ocular finding because of serologic abnormalities in their patient, which were compatible with collagen vascular disease. The presence of identical fundus changes in an otherwise healthy patient with babesiosis confirms their conclusion that nerve fiber layer infarcts occur in this disease. The infarct is presumably related to the procoagulant activity of the infected erythrocyte, which has been demonstrated in vitro.[3]

The ocular abnormality in babesiosis may be useful diagnostically and in differentiation from Lyme borreliosis borne by the same tick. Since nerve fiber layer infarcts are often asymptomatic, ophthalmoscopy is indicated in patients with babesiosis or unexplained hemolytic anemia.

References

1. Gombert, M., Goldstein, E., Benach, J. L., Tenenbaum, M., Grunwaldt, E., Kaplan, M., and Eveland, L.: Human babesiosis. Clinical and therapeutic considerations. JAMA 248:3005, 1982.
2. Ortiz, J. M., and Eagle, R. C.: Ocular findings in human babesiosis. Am. J. Ophthalmol. 93:307, 1982.
3. Goodger, B. V., Rode-Bramanis, K., and Wright, I. G.: Procoagulant activity of *Babesia bovis*-infected erythrocytes. J. Parasitol. 73:1052, 1987.

Sudden Improvement of Visual Acuity After a Retinal Pigment Epithelium Tear

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Retinal pigment epithelium tears have been well documented as a complication of pigment epithelial detachment with age-related macular degeneration. Tearing of detached retinal pigment epithelium with subsequent retraction and exposure of Bruch's membrane and the choriocapillaris may occur spontaneously or after a laser treatment, and usually results in poor visual function. Decreased function prob-

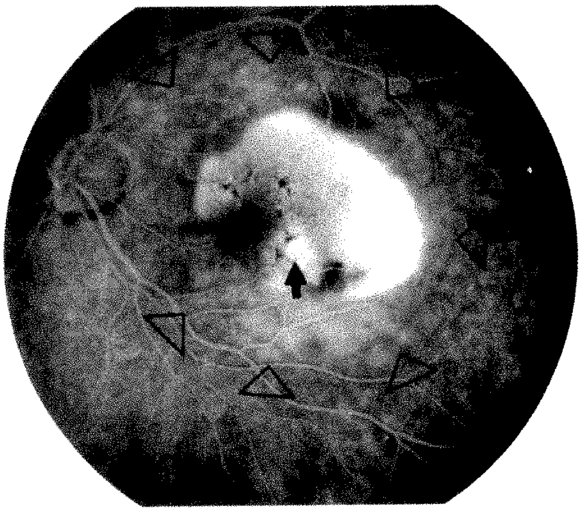

Fig. 1 (Staurenghi, Bottoni, and Orzalesi). Retinal pigment epithelium detachment with an underlying inactive subretinal neovascular membrane (arrow) surrounded by a large shallow detachment of the neurosensory retina (arrowheads).

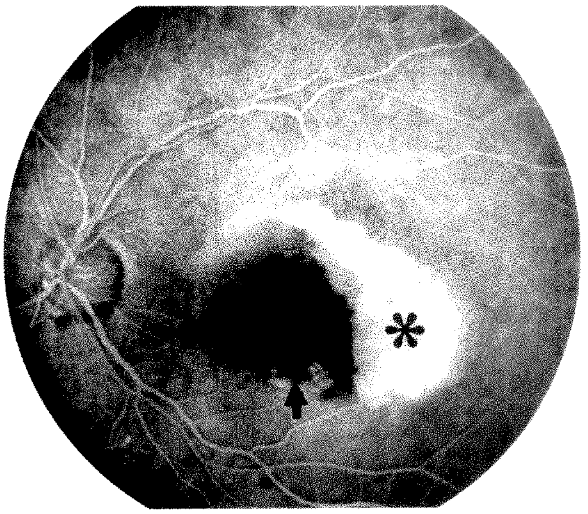

Fig. 2 (Staurenghi, Bottoni, and Orzalesi). Posttreatment retinal pigment epithelium tear. Large hyperfluorescent area corresponds to the bare choroid (asterisk). The hypofluorescent area corresponding to the treated subretinal neovascular membrane appears undetected (arrow).

ably occurs because the anatomic relationships between foveal photoreceptors and retinal pigment epithelium become abnormal.[1]

A 67-year-old woman referred to our retina service had a history of decreased visual acuity and metamorphopsia in the left eye, which lasted several weeks. Visual acuity was R.E.: 20/20 and L.E.: 20/200. Fluorescein angiography showed age-related macular degeneration with hard and soft drusen in the right eye and a 3-disk diameter retinal pigment epithelium detachment surrounding and sparing the foveal avascular zone in the left eye (Fig. 1). Detachment of the neurosensory retina was also present, extending throughout the posterior pole. A focal hyperfluorescent area at the inferior edge of the retinal pigment epithelium detachment (hot spot) was detected and treated after 24 hours with heavy, confluent spots of argon green laser photocoagulation. The patient was reexamined after 15 days. Fluorescein angiography showed absence of any choroidal filling in the area of treatment. Retinal pigment epithelium and neurosensory retina detachments were unchanged. After treatment the visual acuity had remained 20/200. Five days later the patient came to our clinic. She reported a sudden improvement of her vision. Visual acuity had improved to 20/60. Fluorescein angiography showed a retinal pigment epithelium tear outside the macula along the temporal margin of the previously detached retinal pigment epithelium. The serous detachment of the neurosensory retina had disappeared (Fig. 2).

We believed that the improvement of visual acuity was caused by the sudden vanishing of the serous detachment of the neurosensory retina. Subretinal fluid is mainly (70%) resorbed by the retinal pigment epithelium, whereas the remaining 30% is probably driven by the higher oncotic pressure of the choroid.[2] The occurrence of a retinal pigment epithelium detachment is probably connected with the development of a hydrophobic barrier at the level of Bruch's membrane.[3] Either active and passive fluid transport could have been reduced in our patient because of damage to detached retinal pigment epithelium and the hydrophobic transformation of Bruch's membrane. A break of retinal pigment epithelium and Bruch's membrane would allow a free passage of fluid from the retina to the choroid; then the choroidal oncotic pump would play a major role in the resorption of the serous detachment of the neurosensory retina. We considered the early reattachment of this layer to the retinal pigment epithelium to be the cause of the improvement of visual acuity. We believe our case to be different from previously reported cases of surprisingly preserved central vision in tearing of macular pigment epithelium detachment[4] because, in our case, the retinal pigment epithelium tear did not involve the fovea.

References

1. Hoskin, A., Bird, A. C., and Sehmi, K.: Tears of detached retinal pigment epithelium. Br. J. Ophthalmol. 68:513, 1981.
2. Negi, A., and Marmor, M. F.: Quantitative estimation of metabolic transport of subretinal fluid. Invest. Ophthalmol. Vis. Sci. 27:1564, 1986.
3. Pauleikhoff, J. C., Harper, C. A., Marshall, J., and Bird, A. C.: Aging changes in Bruch's membrane. Ophthalmology 97:171, 1990.
4. Finkelstein, D., Bressler, N., Sunness, J., and Yarian, D.: Good visual acuity following pigment epithelial rip through the fovea. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 48.

Radiation Retinopathy After Standard Radiotherapy for Thyroid-Related Ophthalmopathy

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The threshold for retinal damage induced by radiation is believed to be a total dose of 3,000 to 3,500 cGy. Several authors have stated that the standard dose of 2,000 cGy, administered in low daily fractions, will not result in radiation retinopathy.[1,2] The patient described herein developed radiation retinopathy after standard orbital radiotherapy.

A 65-year-old woman with severe Graves' ophthalmopathy had optic neuropathy, which reduced her visual acuity to R.E.: finger counting and L.E.: 20/70. She received 2,000 cGy of orbital irradiation via split beam parallel opposed fields from a 4-MeV linear accelerator over ten equal sessions. The dosimetry curve estimated a maximum of 2,080 cGy delivered to each orbit (Fig. 1). Because her vision failed to improve, she was referred to one of us (J.D.B.). The patient underwent bilateral orbital decompressions 16 months after radiotherapy. Her visual acuity improved to R.E.: 20/50 and L.E.: 20/25. Vision remained stable until three years after orbital radiation when she developed progressive visual loss in her right eye. Fundus examination disclosed bilateral cotton-wool spots, and intraretinal hemorrhages and exudates, with no change in the optic nerves (Fig. 2). A fluorescein angiogram showed extensive capillary nonperfusion. Results of tests for diabetes mellitus, vasculitis, and hypertension were negative.

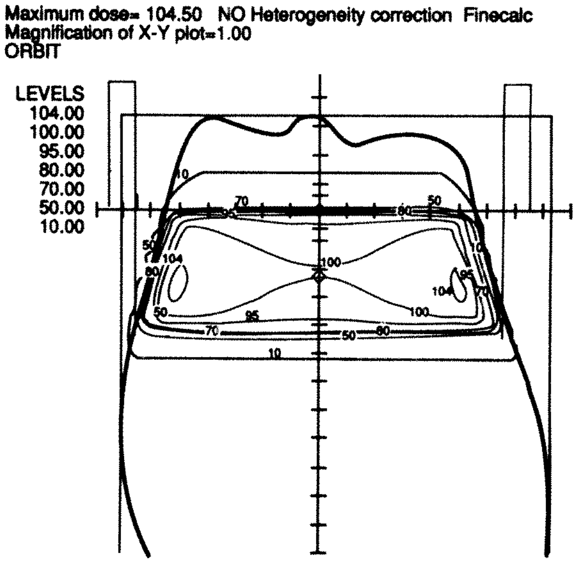

Fig. 1 (Miller, Goldberg, and Bullock). Dosimetry curve for orbital radiation therapy. Percentages of calculated radiation delivered are delineated. Each orbit received a maximum of 104% of the delivered radiation.

Radiotherapy for Graves' ophthalmopathy is often recommended for patients with optic neuropathy or corneal ulceration who cannot receive corticosteroids systemically. Current therapy consists of 2,000 cGy given in ten equal doses. Daily fraction doses greater than 250 cGy may predispose to more tissue injury.[3]

Radiation retinopathy typically manifests between six months and three years after ophthalmic irradiation. It is characterized by cotton-wool spots and intraretinal hemorrhages and exudates. Fluorescein angiography shows significant capillary nonperfusion in affected areas of the retina. Presumably, there is direct retinal microvascular insult from the radiation.[3]

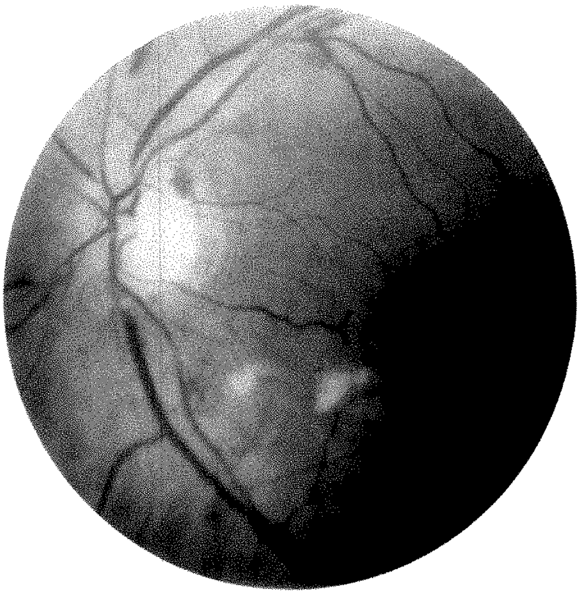

Fig. 2 (Miller, Goldberg, and Bullock). Left eye. Fundus photograph 36 months after completion of radiation therapy demonstrates characteristic cotton-wool spots and intraretinal hemorrhages of radiation retinopathy.

A study of orbital irradiation in Graves' ophthalmopathy described 28 patients who received 2,000 cGy per orbit.[4] No long-term complications were encountered after a mean follow-up of 17 months. Nikoskelainen and Joensuu[5] described 14 patients treated with orbital irradiation for severe Graves' ophthalmopathy. Of six patients who developed retinopathy, four received 3,000 cGy, one received 2,300 cGy, and one received 2,000 cGy. All eight who did not develop retinopathy had total doses of 2,100 cGy or less. However, three patients of this latter group were followed up eight months or less. Petersen and colleagues[2] described 242 patients with Graves' ophthalmopathy treated with 2,000 cGy, none of whom developed radiation retinopathy after median follow-up of either 16 or 34 months.[2]

The clinical findings in our case strongly support the diagnosis of radiation retinopathy. Careful review of the daily treatment record confirmed that dosimetry was accurately calculated and that standard therapy, consisting of a maximum of 2,080 cGy, was delivered to each orbit. This case demonstrates that radiation retinopathy can be a complication of orbital irradiation for Graves' ophthalmopathy, even at radiation levels previously thought to be safe. Patients treated as such require ophthalmic follow-up for a minimum of three years.

References

1. Parker, R. G., and Withers, H. R.: Radiation retinopathy. JAMA 259:43, 1988.
2. Petersen, I. A., Kriss, J. P., McDougall, I. R., and Donaldson, S. S.: Prognostic factors in the radiotherapy of Graves' ophthalmopathy. Int. J. Radiation Oncol. Biol. Phys. 9:259, 1990.
3. Brown, G. C., Shields, J. A., Sanborn, G., Augsberger, J. J., Savino, P. J., and Schatz, N. D.: Radiation retinopathy. Ophthalmology 89:1494, 1982.
4. Olivotto, I. A., Ludgate, C. M., Allen, L. H., and Rootman, J: Supervoltage radiotherapy for Graves' ophthalmopathy. CCABC technique and results. Int. J. Radiation Oncol. Biol. Phys. 11:2085, 1985.
5. Nikoskelainen, E., and Joensuu, H.: Retinopathy after irradiation for Graves' ophthalmopathy. Lancet 2:690, 1989.

Sneezing as an Early Indicator of Allergy to Fluorescein Dye

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Many complications of fluorescein angiography, including severe allergy to the dye, have been reported. Early recognition of allergy combined with prompt treatment can be lifesaving. I treated a patient who had an early indicator of severe allergic reaction that was not previously familiar to me.

A 15-year-old girl had decreased vision in the left eye of one week's duration. She had no significant medical history. The loss of vision was not associated with any pain.

Ocular examination disclosed some hyperemia of the optic nerve in the left eye. There were rare cells in the posterior vitreous.

Because the visual loss was of unknown origin and the optic nerve appeared to be abnormal, a fluorescein angiogram was obtained. Approximately four minutes into the study, the patient began sneezing, approximately 20 times per minute. Two minutes later, she developed dyspnea. She had severe eyelid edema as well as swelling of the tongue. Her lips turned blue.

She was promptly treated with epinephrine 1/1,000 in a dose of 0.3 ml given subcutaneously. Diphenhydramine HCl, 50 mg, was given intramuscularly. She was brought to an emergency room where she was treated with oxygen and corticosteroids intravenously.

The patient did well without further sequelae. After a brief period, she was breathing easily. She was discharged from the emergency room on a regimen of systemically administered corticosteroids as well as diphenhydramine HCl.

Rapid sneezing is an early sign of allergic disease.[1] Some early signs of anaphylaxis include weakness, sweating, sneezing, nasal discharge, or angioedema. This can be followed rapidly by dyspnea, wheezing, or shock. Early recognition of an anaphylactic reaction can be life-saving.

Any location where fluorescein angiography is performed should be supplied with emergency equipment to handle anaphylactic reactions and personnel to manage these emergencies.

Reference

1. Weiszer, I.: Allergic emergencies. In Patterson, R. (ed.): Allergic Disease, Diagnosis and Management. ed. 2. Philadelphia, J. B. Lippincott Company, 1980, p. 381.

Argon Laser-induced Retinal Herniation

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Experimental studies in primates have shown that laser photocoagulation of the retina produced subretinal neovascularization with leakage and pooling of fluorescein dye in 38% to 40% of the lesions.[1] Invariably, these lesions were associated with scar formation and proliferation of the retinal pigment epithelium and choroidal tissue into the subretinal space and retina (Fig. 1).

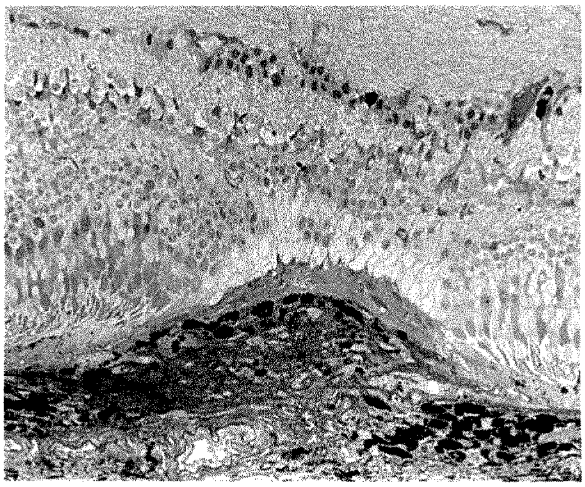

Fig. 1 (El Dirini and associates). Light micrograph of an argon laser-induced lesion showing scar formation and proliferation of the retinal pigment epithelium and choroidal tissue into the subretinal space and retina (× 185).

Recent attempts to reproduce this subretinal neovascularization in a primate model,[2] using a standard argon laser, with the same factors produced lesions with a notably different histologic appearance. Instead of a subretinal scar, the retinal tissue appeared to herniate into the choroid.

We applied eight standard argon laser burns to each eye of a cynomolgus monkey. The lesions were monitored clinically with both fundus photography and fluorescein angiography on days 1 and 3, then every week for six weeks. The eyes were then enucleated, the lesions resected and fixed in half-strength Karnovsky fixative, and sections prepared and stained for light and transmission electron microscopy as previously described.[3]

Clinically, fluorescein angiography disclosed leakage and pooling of dye within three weeks after the argon laser treatment. Light and electron microscopy confirmed the formation of subretinal neovascularization in three of the eight laser lesions in each eye.

However, in another three lesions, an unexpected herniation of retinal tissue into the choroid was observed, and careful study of these sections showed no evidence of subretinal neovascularization within these lesions. The retinal tissue that had herniated through a break in the underlying Bruch's membrane showed areas of vacuolation and degeneration, yet other portions of the tissue remained viable within

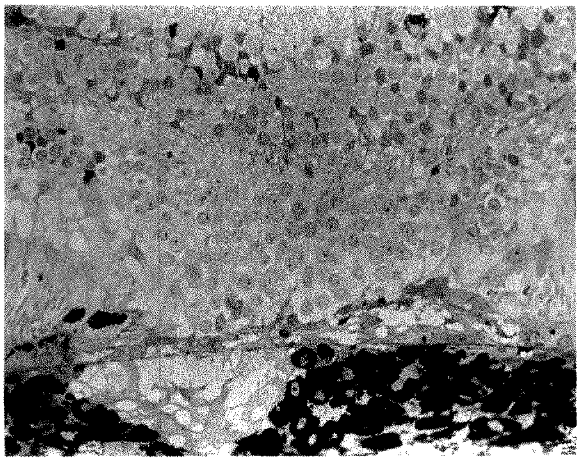

Fig. 2 (El Dirini and associates). Light micrograph of an argon laser-induced lesion showing retinal herniation into the choroid, and degeneration and vacuolation of a portion of the incarcerated retinal tissue, whereas other areas show viable tissue and no evidence of subretinal neovascularization (× 285).

the choroid six weeks after argon laser treatment (Fig. 2).

Multiple overlapping laser photocoagulation burns have been reported to produce a similar peculiar retinal herniation phenomenon.[4] However, the absence of subretinal neovascularization within such lesions is an interesting finding, as neighboring lesions, created in an identical manner, produced typical subretinal neovascularization with leakage and dye pooling and with the characteristic subretinal scar formation.

It thus appears there is a correlation between retinal herniation and the absence of subretinal neovascularization in this animal model. Perhaps the incarceration of retinal tissue in the laser lesions prevents subretinal neovascularization formation, much as envelopment of the subretinal neovascularization by retinal pigment epithelium cells can cause involution, by obliteration of the subretinal space.[5]

References

1. Miller, H., Miller, B., and Ryan, S. J.: The role of retinal pigment epithelium in the involution of subretinal neovascularization. Invest. Ophthalmol. Vis. Sci. 27:1644, 1986.

2. Archer, D. B., and Gardiner, T. A.: Electron microscopic features of experimental choroidal neovascularization. Am. J. Ophthalmol. 91:433, 1981.

3. Pollack, A., Heriot, W. J., and Henkind, P.: Cellular processes causing defects in Bruch's membrane following krypton laser photocoagulation. Ophthalmology 93:1113, 1986.

4. Saedy, M. F., Martini, B., Black, J., Ariyasu, R., Ma, C., Ogden, T. E., and Ryan, S. J.: Herniation of retinal tissue into choroid as a consequence of multiple photocoagulation treatments. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 461.

5. Zhu, Z. R., Goodnight, R., Sorgente, M., Ogden, T. E., and Ryan, S. J.: Morphologic observations of retinal pigment epithelial proliferation and neovascularization in the rabbit. Retina 9:319, 1989.

Immediate Pressure Effects of Nd:YAG Cyclocoagulation

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Transscleral cyclocoagulation with Nd:YAG laser effectively lowers intraocular pressure in patients with intractable glaucoma. This procedure is, however, associated with serious complications including phthisis bulbi and loss of vision.[1] However, it is believed to be safer, better tolerated, and to have fewer complications than cyclocryotherapy.[1-4]

Caprioli and Sears[5] reported acute intraocular pressure increases during the freezing phase of cyclocryotherapy. They found intraocular pressure spikes as high as 60 to 80 mm Hg intraoperatively during the freezing phase. They suggested these pressures could damage already-compromised optic nerves, leading to deterioration in visual fields and visual acuity. Schuman and associates[2] reported delayed intraocular pressure spikes after contact transscleral cycloablation. They found an increase of 8 mm Hg or greater one hour after treatment in 9% of cases and in 6% of cases at day 1 after treatment. Hampton and Shields[3] reported posttreatment intraocular pressure increases in 22% of cases one to two hours after treatment and in 9% at posttreatment day 1.

The purpose of this study was to determine whether an increase in intraocular pressure occurs both during and immediately after noncontact transscleral Nd:YAG cyclocoagulation. We prospectively measured intraocular pressure with a calibrated pneumotonometer in 16 eyes (11 patients) before, during, immediately after, and one hour after treatment. Intraocular pressure was measured three times, and the mean of the three readings was taken as the final intraocular pressure. All patients (16 eyes) had uncontrolled glaucoma of various types despite previous attempts at pressure control, including maximal medical therapy, argon laser trabeculoplasty, filtering surgery, and cyclocryotherapy. Our method of performing noncontact Nd:YAG cyclocoagulation has been reported elsewhere.[1]

With the patient seated at the laser, the pressure was measured as indicated. Treatment was begun and stopped exactly midway through the procedure (after 20 laser burns), and the intraocular pressure was measured immediately. The procedure was then completed, and the pressure was remeasured a third time and then finally one hour after treatment.

Variable increases in pressures were detected during and after treatment: mean preoperative intraocular pressure was 39.7 mm Hg (± 8.6 mm Hg); mean intraoperative intraocular pressure was 42.5 mm Hg (± 13.9 mm Hg); mean immediate postoperative intraocular pressure was 42.3 mm Hg (± 13.9 mm Hg). The mean one-hour postoperative intraocular pressure was 29.5 mm Hg (± 12.5 mm Hg), a statistically significant reduction in intraocular pressure ($P < .005$).

Eight eyes (50%) had an increase in pressure of some kind (that is, during treatment, immediately after treatment, or one hour after treatment). Seven eyes had a pressure increase during treatment. Five of these eyes had pressure increases ranging between 1 and 4 mm Hg (mean, 2.6 mm Hg). Two, however, had pressure spikes above 8 mm Hg: 14 and 49 mm Hg, respectively. Both were back to within 3 mm Hg of prelaser baseline pressure one hour postoperatively. Eight eyes had a pressure spike immediately after treatment. Seven of these eight also had intraoperative pressure spikes. Five of the eight had pressure increases ranging between 1 and 2 mm Hg. Three eyes had pressure spikes above 8 mm Hg: 10, 13, and 49 mm Hg, respectively. In two eyes pressure increased one hour after treatment (3 and 10 mm Hg, respectively). As indicated above, one eye (aniridic glaucoma) had a pressure increase of 49 mm Hg intraoperatively but returned to within 3 mm Hg of baseline pressure at one hour. This same eye required retreatment and again had an intraoperative pressure increase of 14 mm Hg above baseline pressure. The pressure returned to 6 mm Hg below baseline pressure by one hour.

Transscleral Nd:YAG cyclocoagulation has been shown to be effective in humans,[1-4] but recent reports indicate that a significant number of patients lose some vision after treatment.[1] During treatment only two of 16 eyes (12.5%) had pressure spikes above 8 mm Hg. Three eyes (18.75%) had pressure spikes immediately postoperatively.

One hour after laser treatment only one of 16 eyes (6.25%) had a pressure increase of greater than 8 mm Hg. Mean intraocular pressure for the group was significantly lower at one hour than immediately before treatment. It seems likely that the vision loss reported after transscleral cyclocoagulation results only in part because of the perioperative pressure spikes. Our results suggest that vision loss after transscleral cyclocoagulation must also result from other factors such as poor intraocular pressure control, cataract formation, uveitis, macular edema, and the like.

In conclusion, transscleral Nd:YAG cyclocoagulation produces a clinically significant intraoperative pressure spike in a small number of patients. This should be taken into account when the procedure is performed on patients with susceptible optic nerve heads.

References

1. Trope G. E., and Ma, S.: Mid-term effects of neodymium: YAG transscleral cyclocoagulation in glaucoma. Ophthalmology 97:73, 1990.
2. Schuman, J. S., Puliafito, C. A., Allingham, R. R., Belcher, C. D., Bellows, A. R., Latina, M. A., and Shingleton, B. J.: Contact transscleral continuous wave neodymium:YAG laser cyclocoagulation. Ophthalmology 97:571, 1990.
3. Hampton, C., and Shields, M. B.: Evaluation of a protocol for transscleral neodymium:YAG cyclocoagulation in one hundred patients. Ophthalmology 97:910, 1990.
4. Kalenak, J. W., Parkinson, J. M., Kass, M. K., and Kolker, A. E.: Transscleral neodymium:YAG laser cyclocoagulation for uncontolled glaucoma. Ophthalmic Surg. 21:346, 1990.
5. Caprioli, J., and Sears, M.: Regulation of intraocular pressure during cyclocryotherapy for advanced glaucoma. Am. J. Ophthalmol. 101:542, 1986.

Corticosteroid-induced Toxic Optic Neuropathy

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Toxic optic neuropathy is a well-known side effect of the administration of many compounds.[1] Conspicuous among these are chloramphenicol, ethambutol, isoniazid, and sulfonamides. Clinically toxic optic neuropathy is suspected when progressive visual loss of varying severity occurs, color vision is regularly impaired, and cecocentral scotomas are typical findings.[1,2] In most cases, withdrawal of the causative agent is followed by gradual recovery (partial or total) of optic nerve function. Reexposure of the patient to the drug should reproduce the symptoms.

Bullous epidermolysis was diagnosed in a 56-year-old man three years before admittance. The patient had been treated with fluprednisolone (4 mg/day, administered orally). Cutaneous lesions improved but one month after the beginning of the therapy he noticed a progressive loss of vision in his left eye. Therapy was discontinued and visual function improved. He then received four more courses of fluprednisolone, which was discontinued because of visual loss first in the left eye. The right eye was also affected when the therapy was administered for long periods. These visual changes were transient and ceased when the treatment was discontinued. No more ophthalmic details were available., He was admitted to our hospital when proteinuria and moderate renal failure were detected. A Bence Jones type multiple myeloma with secondary amyloidosis was diagnosed. For this reason, he began a four-day regimen of prednisone (160 mg/day, administered orally) and melphalan (15 mg/day). He noticed vision loss which disappeared within a week. When a similar regimen was begun six weeks later, visual loss recurred. When the patient was referred to the ophthalmology service his visual acuity was R.E.: 20/20 and L.E.: 20/40. He had a moderate, left afferent pupillary defect and an enlarged blind spot with a relative cecocentral scotoma with normal peripheral limits in the left visual field. The right visual field was normal. A Farnsworth-Munsell 100 Hue test disclosed a normal reading in the right eye, whereas in the left eye there were 603 errors with a red-green axis. Results of the remainder of the examination were normal, including fundus and optic disk appearance. Neurophysiologic studies were not undertaken. Nine days after therapy was discontinued, visual acuity was R.E.: 20/20 and L.E.: 20/25. No afferent pupillary defect was found, and the Farnsworth-Munsell score was 208 in the left eye, which was still in the red-green axis. Within three months a regimen with no corticosteroids was begun. The patient received melphalan (15 mg/day orally) for four days and a single dose of vincristine (1 mg intravenously) and cyclophosphamide (400 mg intravenously). On the fourth day of treatment, visual acuity was 20/20 in each eye. Results of perimetry and color vision testing were normal. The patient was last seen one year later. Results were similar.

Corticosteroids have been related to a variety of optic nerve disorders including ischemic optic neuropathy,[3] optic disk swelling in corticosteroid-induced pseudotumor cerebri.[4] Our case was consistent with the typical features of direct optic neurotoxicity, not only because of the clinical findings but also because of the close relationship with the causative agent. Fluprednisolone was the corticosteroid used in five courses and prednisolone was used by us in two, with equal toxicity in both. Multiple myelomas and amyloidosis have also been related to infiltrative disorders of the optic nerve. It is unlikely, however, that they caused the visual deficit in our patient. We consider this was a case of toxic optic neuropathy induced by corticosteroids.

References

1. Grant, W. M.: Toxicology of the Eye. Springfield, Illinois, Charles C Thomas, 1974, pp. 49–54.
2. Miller, N. R.: Walsh and Hoyt's Clinical Neuro-ophthalmology, ed. 4. Baltimore, Williams & Wilkins, 1982, p. 299.
3. Demailly, P., and Dureuil, J.: Complications neurophtalmologiques de la corticothérapie. In Demailly, P., Hamard, H., and Luton, J. P. (eds.): Oeil et Cortisone. Paris, Masson & Cie, 1975, p. 338.
4. Braun-Vallon, S., and Aron, J. J.: Accidents

d'hypertension intracrânienne au décours et à l'arrêt des corticothérapies prolongées chez l'enfant. Bull. Soc. Ophtalmol. 12:943, 1961.

Juvenile Cataract Associated With Chronic Diarrhea in Pediatric Cerebrotendinous Xanthomatosis

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Cerebrotendinous xanthomatosis is an autosomal-recessive metabolic disease that is almost never diagnosed in childhood, probably because of the absence of xanthomas in young patients and the absence of abnormalities in routine examinations of blood, urine, and cerebrospinal fluid.[1,2] However, a late diagnosis without therapy is harmful to the patient because the disease has a progressive course, which leads to severe mental and neurologic deterioration.[2]

We diagnosed cerebrotendinous xanthomatosis in young patients by performing specific biochemical studies[3] in children with unexplained bilateral juvenile cataract and a history of chronic diarrhea since infancy.

Case 1

A 6-year-old girl was referred, together with her brother, to the Institute of Pediatrics, University Hospital Nijmegen, because of chronic diarrhea since infancy. Bilateral cataract had been diagnosed three years previously in both patients. Extensive examination in another institution had not led to a specific diagnosis to explain the two unusual features.

Ocular examination of the girl on June 25, 1990, disclosed visual acuity of R.E.: counting fingers at 4 m and L.E.: counting fingers at 2 m. Ocular movements were full, and no nystagmus was noted. Slit-lamp examination showed a bilateral cortical cataract with multiple irregular line-shaped opacities, in addition to a posterior subcapsular cataract that was more dense in the left eye than in the right. The line-shaped opacities had a radial arrangement and were mostly white; however, some were blue. The nucleus of the lens was clear. The ophthalmoscopic findings were normal.

Case 2

Ocular examination on June 25, 1990, of the 12-year-old brother disclosed visual acuity of R.E.: 20/40 and L.E.: 20/25. The ocular findings were the same as those in his sister (Case 1), except that there was no posterior subcapsular opacity in the bilateral cataract.

Although a common cause of the cataract and the diarrhea was a possibility, our search for such an entity yielded no references in the literature. However, during a search in our files of patients with early cataracts, chronic diarrhea was noted in an adult patient in whom cerebrotendinous xanthomatosis had been diagnosed. Gas chromatography was performed in our patients in December 1990 to determine urinary bile alcohols (Figure). The results confirmed the diagnosis of cerebrotendinous xanthomatosis in both children, neither of whom had xanthomas. Chenodeoxycholic acid therapy resulted in a marked reduction of abnormal urinary bile alcohols.

Case 3

A 12-year-old boy was referred to us June 11, 1991, because of a severe decrease of vision caused by the progression of bilateral cataract. The cataracts had been diagnosed by an ophthalmologist three years previously, but did not interfere with vision at that time when bilateral anterior polar cataract was diagnosed. At age 7, when the child underwent an extensive neuropediatric examination because of learning problems, psychomotor retardation of unknown origin was diagnosed. The parents stated that the boy had had chronic diarrhea since infancy.

Visual acuity was R.E.: hand motions at 1 m and L.E.: counting fingers at 4 m. Ocular movements were full, and no nystagmus was noted. Slit-lamp examination of the right lens showed a total white cataract with a capsular fold in the anterior polar region. The left lens showed homogeneously small opacifications, resembling flakes, in the whole lens in addition to a dense anterior polar cataract. The fundus was not visible in the right eye, and indirect ophthalmoscopy showed no abnormality in the left eye.

On the basis of the experience in Cases 1 and 2, that progressive bilateral cataracts associated with a history of chronic diarrhea may be the

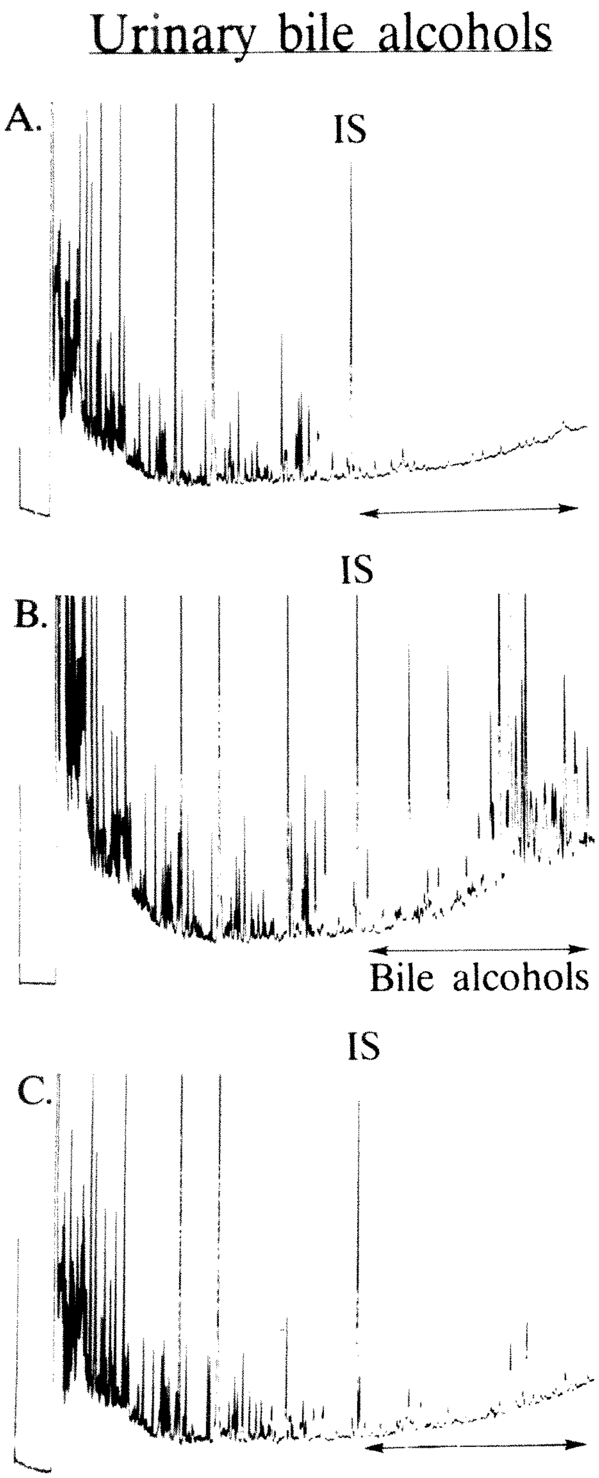

Figure (Cruysberg, Wevers, and Tolboom). Urinary gas chromatography of bile alcohols. A, Normal pattern shows no spikes after internal standard (IS). B, Abnormal urinary bile alcohols in Case 2 at the time of diagnosis of cerebrotendinous xanthomatosis. C, Reduction of abnormal urinary bile alcohols in Case 2 after treatment with chenodeoxycholic acid.

initial clinical signs of cerebrotendinous xanthomatosis, gas chromatography for bile alcohols of urine was performed. Results confirmed the diagnosis of cerebrotendinous xanthomatosis biochemically. Xanthomas were absent in the child.

The results in our three patients confirm that it is possible to diagnose cerebrotendinous xanthomatosis in a patient at a young age by performing gas chromatography for the presence of abnormal bile alcohols in the urine of children with unexplained bilateral cataracts and a history of chronic diarrhea since infancy. Treatment with chenodeoxycholic acid causes an immediate reduction of the excretion of abnormal bile alcohols in the urine. It seems likely that the chronic diarrhea is caused by cerebrotendinous xanthomatosis. At present, we are investigating the pathophysiologic aspects of this symptom.

The risk of cataract caused by severe diarrheal disease has been suggested and denied in different population studies.[4]

We suggest that the finding of bilateral juvenile cataract associated with chronic diarrhea, may represent the earliest clinical manifestation of cerebrotendinous xanthomatosis. Performance of urine gas chromatography in such cases may lead to an earlier diagnosis and a better prognosis of this disabling disease.

References

1. Kuriyama, M., Fujiyama, J., Yoshidome, H., Takenaga, S., Matsumuro, K., Kasama, T., Fukuda, K., Kuramoto, T., Hoshita, T., Seyama, Y., Okatu, Y., and Osame, M.: Cerebrotendinous xanthomatosis. Clinical and biochemical evaluation of eight patients and review of the literature. J. Neurol. Sci. 102:225, 1991.
2. Björkhem, I., and Skrede, S.: Familial diseases with storage of sterols other than cholesterol. Cerebrotendinous xanthomatosis and phytosterolemia. In Scriver, C. R., Beaudet, A. L., Sly, W. S., and Valle, D. (eds.): The Metabolic Basis of Inherited Disease, ed. 6. New York, McGraw-Hill, 1989, pp. 1283-1302.
3. Wolthers, B. G., Volmer, M., van der Molen, J. C., Koopman, B. J., de Jager, A. E. J., and Waterreus, R. J.: Diagnosis of cerebrotendinous xanthomatosis (CTX) and effect of chenodeoxycholic acid therapy by analysis of urine using capillary gas chromatography. Clin. Chim. Acta 131:53, 1983.
4. Bhatnagar, R., West, K. P., Vitale, S., Sommer, A., Joshi, S., and Venkataswamy, G.: Risk of cataract and history of severe diarrheal disease in Southern India. Arch. Ophthalmol. 109:696, 1991.

Bilateral Congenital Absence of Pupillary Aperture

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In an otherwise healthy, newborn infant, the pupillary aperture was not present in both eyes. The patient was of normal gestational age and birth weight and had not received perinatal oxygen. There was no history of intrauterine infection.

The boy was first examined at 20 days of age. The eyes appeared to be microphthalmic. However, there was some evidence of light perception with pursuit movements.

On microscopic examination, the pupils were not present. However, there was a small papilla, displaced slightly in the superonasal quadrant, suggesting pupillary ruff in both eyes (Fig. 1). There was no response to mydriatics. On echographic examination, the axial length was 15 mm in each eye. The lenses were not detected echographically, and the vitreous cavity was clear.

Early surgical intervention was planned to preserve the eye and to salvage some vision. As no pupillary aperture was present, we preferred the limbal to the pars plana approach. Initially, an attempt was made to dilate the iris with blunt instruments in the pupillary region. The lens was not present and completely replaced by fibrous calcified white tissue, pseudophakia fibrosa[1] (Fig. 2). The fibrous material and the iris tissue adherent to it were removed by a vitreous cutter to create a permanent pupillary aperture. No vascular remnant or hemorrhage were observed during the procedure.

Using the same surgical technique three weeks later, we operated on the left eye. The findings were the same as in the right eye.

Mild corneal edema in the right eye disappeared within a few days.

The precise origin of the pupillary anomaly remained unknown. The lenses might have been either undeveloped embryologically or completely resorbed, during the intrauterine period.[1,2]

At postoperative examination, the optic disks were atrophic and totally white in appearance. Both fundi were otherwise normal.

We thought that contracture of fibrous material derived from remnants of tunica vasculosa lentis or, less probably, from intrauterine ocular infection could be the reason for the absence of the pupillary aperture and, consequently, resorption or agenesis of the lens.[1-3]

References

1. Puklin, J. E., and Apple, D. J.: The Retina. Retinoblastoma and leukokoria. In Peyman, G. A., Sanders, R. D., and Goldberg, M. E. (eds.): Principles and Practice of Ophthalmology, vol. 2. Philadelphia, W. B. Saunders Co., 1980, pp. 1512–1517.
2. Scott, R. L., Luis, A., and Taylor, D.: Congenital

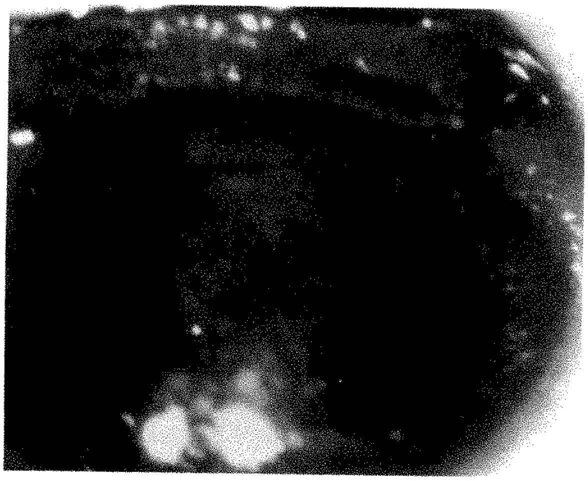

Fig. 1 (Maden and associates). The microscopic aspect of the right eye. The arrow shows the point that corresponds to pupillary region.

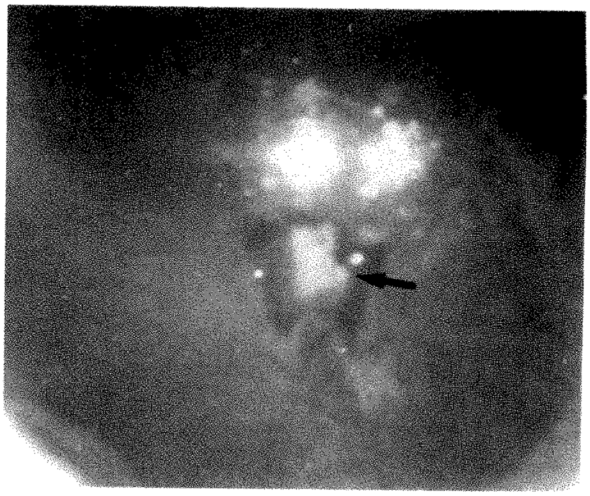

Fig. 2 (Maden and associates). The fibrous material (arrow) behind the iris during the surgical procedure.

idiopathic microcoria. Am. J. Ophthalmol. 106:590, 1988.

3. Vila-Coro, A. A., Mazow, M. L., Holladay, J. T., and Arnoult, J. B.: Congenital idiopathic microcoria. Am. J. Ophthalmol. 107:439, 1989.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Correlation of the Blind Spot Size to the Area of the Optic Disk and Parapapillary Atrophy

EDITOR:

In the article, "Correlation of the blind spot size to the area of the optic disk and parapapillary atrophy," by J. B. Jonas, G. C. Gusek, and C. Fernandez (Am. J. Ophthalmol. 111:559, May 1991), the authors state that there is a statistically significant difference between the blind spot size of glaucomatous and normal eyes, and that these findings are correlated to the optic disk size and to the parapapillary chorioretinal atrophy. Moreover, they found that the difference was larger using I_{4e}, I_{3e}, and I_{2e} isopters compared to the III_{4e} isopter. However, for their research, the authors used manual kinetic perimetry, which may not be the ideal technique, because of human variability and subjectivity. In testing such a small field area, slight changes in technique, particularly a nonhomogeneous stimulus velocity, could cause significant differences in measured blind spot area. Conversely, the authors correctly state that the automated Octopus program G1 is not suitable for detection of a glaucomatous enlargement of the blind spot.

Using a Humphrey Field Analyzer 60-point grid custom test, we obtained similar findings[1,2]: pericecal sensitivity was markedly depressed in eyes with ocular hypertension and early open-angle glaucoma as compared to normal eyes. The absolute density nucleus of the blind spot, however, was not enlarged. Starting from these data, we studied the possibility of using some test points from a widely adopted standard program to show the same findings without any increase in the test time.[3] Again, using 12 points from the Humphrey Field analyzer C-30-2 threshold program, we found a statistically significant difference between mean sensitivity of glaucomatous and normal eyes. A "pericecal index," whose usefulness is at present under investigation, was then created.

Jonas and associates' results and our data, although obtained with different techniques, are substantially in agreement and show that the study of the blind spot, often disregarded in computerized automated perimetry, could be of some interest in the visual field examination of glaucomatous patients.

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GIOVANNI DELLA MEA, M.D.
FLAVIA MIANI, M.D.
CLAUDIA TOSONI, M.D.
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References

1. Brusini, P., Della Mea, G., and Tosoni, C.: Pericoecal light sensitivity in suspected glaucoma and in early primary open-angle glaucoma. New Trends Ophthalmol. 1:235, 1986.

2. ———: Analisi perimetrica computerizzata dell'area pericecale nell'otticopatia glaucomatosa iniziale. Proc. Soc. Oftalmol. Ital. Nuova Casa Ed. Cappelli S.p.A., 1988, pp. 273–278.

3. Brusini, P., Della Mea, G., Miani, F., and Tosoni, C.: "L'indice pericecale" nella diagnosi precoce di glaucoma ad angolo aperto. Min. Oftalmol. 32:59, 1990.

Reply

EDITOR:

We appreciate the thoughtful comments of Dr. Brusini and his associates, and we agree with their statements. Just as we, they found a marked difference in blind spot size between normal subjects and glaucoma patients, which emphasizes that the evaluation of the blind spot could be of some interest in the perimetric examination of glaucoma patients.

JOST B. JONAS, M.D.
GABRIELE C. GUSEK, M.D.
MARTIN C. FERNANDEZ, M.D.
Erlangen, Germany

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Color Atlas of Lens Implantation. Edited by Piers Percival. St. Louis, Mosby Year Book, 1991. 317 pages, index, illustrated. $140

Reviewed by M. CATHLEEN SCHANZER
Memphis, Tennessee

This text successfully brings together the evolution of surgical techniques involving cataract extraction and intraocular lens implantation in outstanding atlas form. The authors thoroughly describe the progression of cataract surgery from the intracapsular technique to the present popular phacoemulsification technique, demonstrating different methods of wound formation, astigmatism control, capsulotomy including capsulorhexis, cataract removal, and intraocular lens fixation. There is an extensive review of the endocapsular technique of phacoemulsification, and there are special sections on glaucoma, pediatrics, severe myopia, microphthalmia, and corneal dystrophies.

Novice phacoemulsification surgeons will appreciate the recommendations on the type of patients to choose for those first stressful cases and the basic warnings about potential problems. There is an easy-to-follow, step-by-step guide for the preoperative preparation of patients. Additionally, there are simple and clear diagrammatic explanations of different phacoemulsification techniques. Tips on corticonuclear bowl removal and more intraoperative photographs would have been of added benefit.

There is a good review of the various irrigating solutions used intraoperatively. The section on lens implantation and postoperative care includes anterior chamber intraocular lens techniques and contraindications to lens implantation. It reviews iris-fixated lenses, which is of historical interest, but has limited clinical relevance. The trend toward capsulorhexis and capsular fixation is stressed, and the clinical example of the continuous circular capsulectomy is excellent. The experienced phacoemulsification surgeon will find the endocapsular technique well illustrated and the intraocular lens suturing technique easy to follow. Additionally, some possible future techniques are discussed, including excimer laser phaco-ablation.

This text begins with an overview of cataract surgery and then proceeds to the surgical technique and intraoperative complications, followed by lens implantation and postoperative care. The preoperative preparation and intraocular lens contraindications are not addressed until later. Despite this sequence, the text is easy to read and enjoyable to browse through. The references at the end of each chapter are invaluable.

Overall, the Color Atlas of Lens Implantation is a well organized and comprehensive review of cataract surgery and intraocular lens implantation. I recommend it without reservation.

Eye Surgery: An Introduction to Operative Technique. ed. 2. By Georg Eisner. Translated by Terry C. Telger. New York, Springer-Verlag, 1990. 317 pages, illustrated. $149

Reviewed by MARK J. MANNIS
Sacramento, California

Anyone who has patiently taught a novice ophthalmic surgeon how to do a new procedure knows all too well how much lip-biting goes on behind the surgical mask as the beginner tentatively makes some classic surgical maneuver. The clumsiness betrays a lack of understanding of how precisely that maneuver should be performed. Even the most intuitive of novice surgeons knows that mature technical skill comes through a series of conscious or unconscious "micro-revelations" about how instruments are best deployed, how tissue is most efficiently maneuvered, and how suture material is optimally handled. In this light, it seems odd there are hardly any surgical texts that deal directly with basic principles of surgical technique the way Dr. Eisner does in this remarkable volume.

The author intends this book to be a "grammar" of ocular surgery. He draws on the analogy that learning a language is needlessly laborious if the student practices the language without any knowledge of its basic structure. Learning the grammar of surgery, he posits, will shorten and enhance the learning process.

This book approaches the geometrical and physical principles on which surgical instrumentation, technique, and tissue properties are based. It concentrates on standard procedures in the anterior segment of the eye, which are usually performed on normal tissue in its normal anatomic position.

Divided into ten sections, the text begins with a discussion of "tissue tactics": grasping, dividing, and uniting tissues. This is followed by a section on "spatial tactics": maintaining or augmenting tissue spaces to create room for micromanipulations within the eye. Although some parts of these two sections are largely theoretical, many of the insights have great practical value, especially for clarifying the reasons for common errors of the novice. Particularly useful are the discussions dealing with the proper handling of various fluid types in the eye and the application of mechanical, energy-using instruments.

The remaining sections include preparation of the operating field, conjunctival corneal and scleral surgery, ciliary body surgery, iris surgery, operations on the lens, and anterior vitrectomy. Unlike other surgical texts, which describe procedures in a how-to manner, this book concentrates on the specific problems and solutions encountered on the basis of the tissue type and the application of tissue-specific tactics. The approach is much like Julia Childs' book about how to peel, dice, blanch, and broil, a book that has no recipes for specific dishes, but says a lot about technique. These chapters include some of the finest surgical advice in the book.

The clearly written text is augmented by 546 lucid three-color illustrations by Peter Schneider, which beautifully illustrate the descriptions. If there are any negative points to be made about this book, they might be the absence of an index, and the omission of the surgical principles of vitreoretinal surgery, which was deliberate and is explained in the forward.

This text is important reading for the beginning surgical resident in ophthalmology and is an invaluable tool for the teacher of ophthalmic surgery. It provides a practical roadmap to ocular surgery for the manually skilled surgeon as well as the slightly less naturally gifted. By analyzing in detail the techniques that are often only glimpsed through a haze of intuition, Dr. Eisner has provided us with a rational understanding of each step of the surgery we perform.

Eye Trauma. By Bradford J. Shingleton, Peter S. Hersh, and Kenneth R. Kenyon. St. Louis, Mosby Year Book, Inc., 1991. 427 pages, index, illustrated. $99

Reviewed by STEVEN R. BENNETT
Minneapolis, Minnesota

The authors set out to create a comprehensive text that will also serve as a reference work, and they have for the most part, succeeded. The chapters are well written and have fairly complete discussions of patient management. Surgical details are offered, together with line drawings of surgical techniques. These chapters will be helpful to the beginning ophthalmology resident trying to handle ocular trauma in an emergency room, and also to experienced practitioners looking for details to refresh their memory on a specific procedure. The chapters on suturing corneal lacerations are particularly well written, with clear discussions and illustrations of techniques to handle complex lacerations to minimize scarring and astigmatism.

My only complaint is that some of the chapters are dogmatic in tone. In a field as complex as trauma, and with little in the way of definitive well-controlled trials, it is difficult to be dogmatic. In general, the recommendations are well thought out and reasonable, but they may not be the only acceptable approaches. Occasionally, a dogmatic statement is even contradicted within the book. For example, on page 23 the authors state, "No ointment or topical medication should be administered to any patient with a suspected rupture of the globe or open wound of the eye," whereas on page 43, in discussion of patients with suspected ruptured globes the authors state "use topical antibiotic drops when no uveal prolapse or only minimal iris prolapse is seen." Both of these are reasonable approaches but may be too emphatically stated, especially if interpreted by a plaintiff's attorney. Perhaps dogma is the price that must be paid to achieve conciseness in a complicated field.

The text is well organized and contains valuable information. It will be particularly helpful to the ophthalmology resident, who must evaluate, triage, and begin treatment in complicated cases with eyelid, anterior segment, as well as posterior segment injuries. By discussing the modern approaches to ocular trauma from all angles, this text is a valuable addition to the libraries of residents and general ophthalmologists, as well as emergency room physicians and ophthalmic subspecialists. I can wholeheartedly recommend the book to any practitioner handling ocular injuries.

Eyelid Surgery. By Earl Rathbaum. Boston, Little, Brown & Co., 1990. 290 pages, index, illustrated. $150

Reviewed by Steven Pratt
La Jolla, California

This excellent book "presents the current status of the procedures Doctor Rathbaum finds useful in eyelid surgery." The author acknowledges the profound influence on his techniques by two outstanding individuals in the field of ophthalmic plastic and reconstructive surgery, Crowell Beard and the late Marvin Quickert.

The text is divided into ten chapters: Eyelid Anatomy, Basic Techniques, Entropion, Cicatricial Entropion and Trichiasis, Ectropion, Eyelid and Canthal Reconstruction, Eyelid Trauma, Blepharoplasty and Brow Elevation, Blepharoptosis, and Eye Retraction. Included in these sections are numerous excellent clinical photographs (preoperative-intraoperative-postoperative) and easy-to-understand illustrations.

The author gives a comprehensive discussion of the pathophysiologic factors responsible for eyelid malpositions, thus providing a sensible approach to the correct operative choice involved in alleviating such disorders. Where appropriate, multiple procedures are discussed. At the end of each chapter is an excellent list of references from a diversified, credible group of authors.

Dr. Rathbaum's description of various operative techniques is superb. As a result, the text, when coupled with the photographs and illustrations, leaves the reader with a clear understanding of the methods described. A chapter on basic techniques gives the reader a good summary on such subjects as skin grafts, full-thickness eyelid repair, traction sutures, and skin suturing techniques.

This is an excellent reference book for ophthalmology residents and fellows, ophthalmologists, general plastic surgeons, dermatologists, otolaryngologists, and oculoplastic surgeons. The text is easy to understand, concise yet comprehensive, and well-organized.

Scanning Laser Ophthalmology and Tomography. By J. E. Nasemann and R. O. W. Burk. Lombard, IL, Quintessence Publishing Co., Inc., 1991. 271 pages, index, illustrated. $140

Reviewed by Karen Joos
and Sohan Singh Hayreh
Iowa City, Iowa

This collection of papers was presented at the First International Symposium on Scanning Laser Ophthalmoscopy and Tomography in Munich in July 1989. Quantitative diagnostic imaging with a laser is an expanding research area in ophthalmology. The book is divided into two sections: Scanning Laser Ophthalmoscopy, which evaluates the eye in two dimensions, and Scanning Laser Tomography, which generates multiple thin-sections through a structure that can be reconstructed for three-dimensional analysis.

The section on scanning laser ophthalmoscopy deals first with terminology and technical aspects of scanning laser imaging, and then considers the study of the following topics: (1) microperimetry and electrophysiology; (2) three-dimensional study of the vitreous; (3) preliminary results of ophthalmic biomicroscopy of ocular structures by this technique; (4) fluorescein angiography; (5) methods used to analyze the images and measure the transit time in individual retinal vessels as well as the arteriovenous circulation times; (6) quantification of retinal blood-flow parameters in fluorescein angiograms; (7) preliminary studies on choroidal abnormalities by using indocyanine green; (8) proposal for the use of scanning laser perfusion videoangiography to evaluate the retinal and choroidal circulation; (9) quantitative fundus reflectometry using this technique and its limitations; and (10) use of the scanning laser ophthalmoscope as an imaging retinal densitometer, for static fundus-controlled perimetry, and for measuring eye movements in three dimensions and monitoring visual target movements directly on the retina.

The section on scanning laser tomography deals with the following subjects: (1) three-dimensional optic disk topography (its structural analysis, the reproducibility and accuracy of the measurements, factors influencing three-dimensional data in follow-up studies, effects of lowering intraocular pressure on disk topography, the problem of reference plane definition for cup-volume measurements, and capability of imaging the glaucomatous optic disk and anterior chamber; (2) retinal macular topography; (3) disturbances of the visual system after laser tomographic scanner measurements; (4) quantitative three-dimensional measurements of the eye in vivo; (5) perspectives and limits of three-dimensional fundus microscopy; and (6) microtopography of retinal structures.

Each chapter includes details of a specific research protocol, equipment, results, and discussion. Some chapters include mathematical formulas that may have been vital for the project, but are too technical for the reader with only a general interest in possible applications of ophthalmoscopic scanning laser imaging. Graphs and comparative fundus photographs illustrate the section on scanning laser ophthalmoscopy. The differences described in some photographs are subtle or not distinguishable. The scanning laser tomography section is well illustrated although red-green glasses, not provided, are required for full appreciation of a few photographs. About half of the chapters are extensively referenced for further reading.

Scanning laser ophthalmoscopy and tomography are promising quantitative methods for noninvasively evaluating ocular structures and function. Advantages include the use of lower light intensities than standard fundus photography, and the ability to examine the fundus through small pupils. Disadvantages include the need for extensive data processing and image analysis capabilities, and extremely expensive equipment, priced well out of reach for most investigators and clinicians. As research prototypes evolve with further refinement, these instruments will probably become cheaper and more commonly used in the clinical examination of patients. The various research applications described or proposed are intriguing, and this book is recommended to anyone interested in exploring the capabilities of this technology in ophthalmology.

The Book List

Case Presentations in Medical Ophthalmology. By Jack J. Kanski and Teifi E. James. Stoneham, MA, Butterworth/Heinemann, 1991. 116 pages, index, illustrated. $24.95

Cataract Biochemistry Epidemiology and Pharmacology. By John Harding. New York, Chapman & Hall, Inc., 1991. 333 pages, index, illustrated. $139.95

Developments in Ophthalmology: Evolution of Microsurgery, Vol. 22. Series Editor W. Straub; editor Ph. Sourdille. Switzerland, S. Karger AG, Basel, 1991. 168 pages, index, illustrated. $136

The Fine Art of Prescribing Glasses, Without Making a Spectacle of Yourself; ed. 2. By Benjamin Milder and Melvin L. Rubin. Gainesville, FL, Triad Publishing Company, 1991. 526 pages, index, illustrated. $78

From Pigments to Perception: Advances in Understanding Visual Processes. Edited by Arne Valberg and Barry B. Lee. New York, Plenum Publishing Corporation, 1991. 484 pages, index, illustrated. $120

Glaucoma Surgical Techniques. Edited by Richard P. Mills and Robert N. Weinreb. San Francisco, American Academy of Ophthalmology, 1991. 180 pages, index, illustrated. $55 for non-members; $40 for members

International Anesthesiology Clinics: Recovery from Anesthesia. By Philip W. Lebowitz. Boston, Little, Brown and Company, 1991. 121 pages, index, illustrated. $81 per quarter

Saunders Ophthalmology Word Book. By Joyce Adams. Philadelphia, W. B. Saunders, 1991. 362 pages. $23.95

A Text and Atlas of Strabismus Surgery. By Renee Richards, Steven Greenberg, and J. Thomas Herbert. Baltimore, Williams & Wilkins, 1991. 226 pages, index, illustrated. $150

Meetings

Fourteenth Biennial Meeting of the Association of Ophthalmic Alumni of the Armed Forces Institute of Pathology

The 14th biennial meeting of the Association of Ophthalmic Alumni of the Armed Forces Institute of Pathology took place in Washington, D.C., June 28–30, 1991. The meeting was opened by the chairman, Robert Levine. The program director was Ian McLean.

The following alumni presented cases: Ahmed Hidayat (Washington, D.C.), Intracytoplasmic epithelial corneal dystrophy; John Varga (Washington, D.C.), Posterior polymorphous corneal dystrophy of Schlichting; David Cogan (Bethesda, Maryland), Two cases of atypical Reis-Buckler corneal dystrophy; Henry Perry (Rockville Center, New York), *Fusarium* keratitis; Shelly Greenberg (Washington, D.C.), Complex choristoma of the central cornea; Harold Rodman (Washington, D.C.), Sebaceous gland carcinoma of eyelid and conjunctiva; Curtis Margo (Gainesville, Florida), In situ sebaceous carcinoma of conjunctiva and meibomian glands; Victor Elner (Ann Arbor, Michigan), Eyelid Merkel cell carcinoma with sebaceous differentiation; Jacob Pe'er (Jerusalem, Israel), Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) with involvement of four eyelids; Moshe Lahav (Boston, Massachusetts), Von Hippel-Lindau disease; Jerry Shields (Philadelphia, Pennsylvania), Neovascular glaucoma secondary to Coats' disease; Marilyn Kincaid (St. Louis, Missouri), Retinoblastoma without calcification; Guy Allaire (Montreal, Quebec, Canada), Congenital orbital teratoma; Bruce Johnson (Pittsburgh, Pennsylvania), Congenital diffuse neurofibroma of the orbit; Robert Levine (Chicago, Illinois), Congenital meningoencephalocele of the orbit; Selwa Al-Hazzaa (Baltimore, Maryland), Uveal involvement in systemic intravascular (angiotrophic) lymphoma; Miguel Burnier, Jr. (Bethesda, Maryland), Primary intraocular lymphoma; Richard O'Grady (Chicago, Illinois), Immunoblastic lymphoma masquerading as an inflammatory lid mass; J. Oscar Croxatto (Buenos Aires, Argentina), Malignant melanoma of the conjunctiva following radiation therapy of retinoblastoma; Mark Tso (Chicago, Illinois), Bilateral malignant melanoma of the choroid; Panfilo de la Cruz, Jr. (Manila, The Philippines), Diffuse and necrotic uveal melanoma with extraocular extension; Jose Cursino (São Paulo, Brazil), Intraocular malignant melanoma with conjunctival and orbital involvement; Paul Chen (Washington, D.C.), Uveal melanoma in a black person; Walter Stafford (St. Louis, Missouri), Unusual uveal malignant melanoma; David Bardenstein (Cleveland, Ohio), Primary orbital melanoma in a 22-month-old girl; W. Richard Green (Baltimore, Maryland), Lacrimal gland adenocarcinoma with mucinous and sebaceous differentiation; Joel Kopelman (New York, New York), Adenoid cystic carcinoma of the lacrimal gland; Charles Specht (Washington, D.C.), Intraorbital varix with thrombosis; Francis LaPiana (Washington, D.C.), Orbitofrontal cholesterol granuloma; Abbot Spaulding (Cincinnati, Ohio), Squamous cell carcinoma of lid invading the eye and orbit; Michael Jalali (South Plainfield, New Jersey), Kearn-Sayre syndrome; Narsing Rao (Los Angeles, California), Disseminated cryptococcosis in AIDS; Seymour Brownstein (Montreal, Quebec, Canada), Bilateral *Aspergillus* endophthalmitis. An unsuspected clinical diagnosis; Victor Curtin (Miami, Florida), Sympathetic ophthalmia ten years after intraocular foreign body injury; Ian McLean (Washington, D.C.), Localized Wegener's granulomatosis.

The following alumni contributed cases but were not present: Gerald Christensen (San Diego, California), Large cell lymphoma of the eye and central nervous system (the GUN syndrome); Dario Savino Zari (Caracas, Venezuela), Melanoma of the conjunctiva in a black person; James Caya (Milwaukee, Wisconsin), Orbital extension in a patient with severe necrotizing sclerouveitis due to Wegener's granulomatosis; Richard Smith (Albany, New York), Uveal melanoma; Bon Sool Koo (Seoul, Korea), Panuveitis in congenital syphilis; Douglas Cameron (Minneapolis, Minnesota), Alveolar soft part sarcoma with involvement of the episclera.

The following alumni were also present: Joseph Berkow (Baltimore, Maryland), and Michael Mund (Clifton, New Jersey).

The topic of the 1993 meeting will be genetic and metabolic disease. Officers for 1991–1993 are Curtis Margo, president; Richard Green, program chairman; and Harold Rodman, secretary-treasurer.

HAROLD RODMAN

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

The development of cataract in children as a late side-effect of bone marrow transplantation. Calissendorff, B., Bolme, P.*, and el Azaz, M.: Bone Marrow Transplant. 7:427, 1991.

CATARACT, MALIGNANCY, TOTAL BODY IRRADIATION

Three children with hematologic malignancies, seven children with severe aplastic anemia, and four children with other nonmalignant diseases were monitored for cataract development after bone marrow transplants. The children with hematologic malignancies received total body irradiation of approximately 10 Gy in one session with no shielding of the eyes. The children with aplastic anemia or other nonmalignant diseases received either no irradiation or a reduced dose of 8 Gy with shielding of the eyes. After three years, all patients who had bone marrow transplants for hematologic malignancies had developed lens opacifications. No patients in the other groups had any clinical signs of cataract development. No relationship between cataract development and corticosteroid treatment for graft-vs-host disease was observed. In these patients, it appeared that total body irradiation given in one session without shielding of the eyes was the main cause of cataract development after bone marrow transplantation.—Michael A. Kass

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Phenylketonuria does not cause cataracts. Pitt, D. B.*, and O'Day, J.: Eur. J. Pediatr. 150:661, 1991.

CATARACT FORMATION, PHENYLKETONURIA

In an attempt to confirm the association between phenylketonuria and cataract formation, adults who had untreated phenylketonuria were examined. The patients ranged in age from 28 to 71 years. Three of the 46 patients (6.5%) had cataracts. This prevalence was similar to that in the general age-matched Australian population and in a control series of disabled adults. Only two of the patients with phenylketonuria and cataracts could be examined by slit-lamp biomicroscopy. The findings suggested that the cataracts may have been caused by prolonged use of phenothiazines in these patients. Thus, the authors were unable to confirm the association between phenylketonuria and cataract development.—Michael A. Kass

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Investigations on diathermy for anterior capsulotomy. Hausmann, N.*, and Richard, G.: Invest. Ophthalmol. Vis. Sci. 32:2155, 1991.

ANTERIOR CAPSULOTOMY, INTRAOCULAR DIATHERMY

A straight, bipolar, high-frequency, diathermy probe was used to perform anterior capsulotomy. In 25 patients with intumescent or mature cataractous lenses, the anterior capsule was cut with this instrument. The instrument was initially passed from the 6 to 12 o'clock meridian in a clockwise fashion and then passed from the 6 to 12 o'clock meridian in a counterclockwise fashion. The remainder of the cataract extraction was performed in standard fashion. The diathermy technique resulted in a smooth capsulotomy that did not tear during nucleus expression. During diathermy, capsulotomy aqueous humor temperature increased from a mean of 29.1 C to a mean of 33.4 C. Over the subsequent 12 months, corneal endothelial cell loss averaged 10% in these patients, which was similar to the authors' general experience with standard capsulotomy techniques.—Michael A. Kass

*Department of Ophthalmology, Landeskrankenhaus Feldkirch, A-6807 Austria.

Comparison of retrobulbar and periocular injections of lignocaine by computerised tomography. Ropo, A.*, Nikki, P., Ruusuvaara, P, and Kivisaari, L.: Br. J. Ophthalmol. 75:417, 1991.

RETROBULBAR ANESTHESIA, PERIBULBAR ANESTHESIA

Ten patients undergoing cataract surgery were given a local anaesthetic with lignocaine solution which was mixed with iohexol contrast medium. The location of the needle and the substance injected was determined by computerised tomography following retrobulbar or periocular anaesthesia. The retrobulbarly inserted needles were within the muscle cone, directed towards the optic foramen. The periocular needles were outside the muscle cone, tangentially along the orbital floor or pointing slightly upwards. After the retrobulbar injection the contrast medium was seen within the cone immediately after the injection and outside the cone as early as 3 minutes after the injection. With the periocular technique, however, diffusion of the anaesthetic in the opposite direction (that is, into the muscle cone) was rapid. The contrast medium was identified inside the muscle cone 2 minutes after the injection. Compression with an intraocular pressure reduction device after both of these techniques prevented exophthalmos. It is concluded that retrobulbar-like anaesthesia can also be induced by an appropriate periocular technique.—Authors' abstract

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Long-term treatment effects in patients with bilateral retinoblastoma: ocular and mid-facial findings. Messmer, E. P.*, Fritze, H., Mohr, C., Heinrich, T., Sauerwein, W., Havers, W., Horsthemke, B., and Höpping, W.: Graefe's Arch. Clin. Exp. Ophthalmol. 229:309, 1991.

RETINOBLASTOMA, RADIATION THERAPY, LONG-TERM VISUAL ACUITY, FACIAL MALFORMATION

A total of 99 patients with bilateral retinoblastoma who had been treated between 1965 and 1982 were reexamined in April 1988 to study the late effects of treatment. Their median age at the follow-up visit in 1988 was 16 years (range, 6–27 years), and the median follow-up was 15 years (range, 6–26 years). All patients underwent a full eye examination, morphometric measurements of the mid-face and genetic counselling. Each eye or orbit and the corresponding side of the patient's mid-face were evaluated separately, resulting in 198 data sets from 99 individuals. Subjects were divided into four treatment groups according to whether photo- and cryocoagulation, enucleation, radiation therapy or various combinations thereof were used. In all, 81 eyes had a visual acuity of > 0.4 (in 23 of these, however, only with low-vision aids). Within a dose range of 36–51 Gy, the location of the tumor (36%) or cataract (15%) were the main factors responsible for poor visual acuity, whereas radiation retinopathy and/or optic neuropathy occurred in only three cases. Cataracts were more frequently observed following orthovoltage as compared with megavoltage therapy ($P = 0.012$). A total of 72 eyes had been enucleated and had not received radiation therapy at any time. Cosmetic results (as measured by several parameters) in these cases were significantly better then those in 28 subjects who underwent combined radiation therapy and enucleation. As defined by various subjective as well as objective findings, mid-facial hypoplasia occurred significantly more often following orthovoltage as compared with megavoltage therapy.—Authors' abstract

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Eyedrop instillation for reluctant children. Smith, S. E.*: Br. J. Ophthalmol. 75:480, 1991.

EYEDROP ADMINISTRATION, CHILDREN

Many children refuse to allow instillation of therapeutic eyedrops. A new technique of eyedrop administration was assessed in which eyedrops were placed in the inner canthus of patients lying in a face-up position with the eyes tightly closed. The eyelids were then opened. This technique was assessed in healthy adults using pilocarpine eyedrops. Pupillary responses were measured with an infrared pupillometer. Using this technique, the mean pupillary response was 66%, which was as great as that obtained by conventional instillation. This approach may be useful in some children who are afraid of standard eyedrop administration.—Michael A. Kass

*Department of Clinical Pharmacology, St. Thomas's Hospital, London SEI 7EH.

Can physician education lower the cost of prescription drugs? A prospective, controlled trial. Frazier, L. M.*, Brown, J. T., Divine, G. W., Fleming, G. R., Philips, N. M., Siegal, W. C., and Khayrallah, M. A.: Ann. Intern. Med. 115:116, 1991.

HEALTH CARE COST, PHYSICIAN EDUCATION

Fifty-one interns were randomly assigned to a control group or to an education intervention group that underwent a training program consisting of a manual of comparative drug prices, two feedback reports, and weekly reminders concerning drug costs. The prescriptions written by the interns were reviewed over the next eight months. Physicians in the intervention group generally prescribed less expensive drugs. The interns in the intervention group also prescribed more medication per prescription, thereby reducing dispensing fees. The educational program was well received by the physicians. This relatively simple educational intervention can help physicians reduce their patients' drug expenses and may serve as a model for incorporating cost information into physician education.—Michael A. Kass

*Box 2914, Duke University Medical Center, Durham, NC 10710.

A prospective study of aspirin use and primary prevention of cardiovascular disease in women. Manson, J. E.*, Stampfer, M. J., Colditz, G. A., Willett, W. C., Rosner, B., Speizer, F. E., and Hennekens, C. H.: JAMA 266:521, 1991.

CARDIOVASCULAR DISEASE, MYOCARDIAL INFARCTION, ASPIRIN USE

Two large trials in which patients were randomly assigned have suggested that aspirin use reduces the incidence of myocardial infarction in men. However, the use of aspirin in women has not been well studied. Coronary artery disease, stroke, and cancer had not been diagnosed in a cohort of 87,678 34- to 65-year-old registered nurses at initial examination. Over the subsequent six years 240 nonfatal myocardial infarctions, 146 nonfatal strokes, and 130 deaths caused by cardiovascular disease were documented. Among women who reported taking one to six aspirin per week, the age-adjusted relative risk of a first myocardial infarction was 0.68 (95% confidence interval, 0.52 to 0.89, P = .005) as compared with those women who took no aspirin. After adjustment for risk factors for coronary disease, the relative risk was 0.75 for women who took aspirin. For women aged 50 years and older who took aspirin, the age-adjusted relative risk was 0.61. No alteration in the risk of stroke was noted. The use of one to six aspirin per week appears to be associated with the reduced risk of first myocardial infarction in women.—Michael A. Kass

*Channing Laboratory, 180 Longwood Ave., Boston, MA 02115.

Ultrasonographic, three-dimensional scanning for determination of intraocular tumor volume. Jensen, P. K.*, and Hansen, M. K.: Acta Ophthalmol. 69:178, 1991.

INTRAOCULAR TUMOR, IMAGE ANALYSIS

To measure the volume of intraocular masses, an ultrasonographic three-dimensional scanning system was developed that operated by an axial, back and forth, half-turn rotation of a commercial sector scanning transducer. This device was applied directly to a patient's closed eyelids. Control of movement, data acquisition, and image analysis were accomplished by means of a microcomputer and application-specific software. The elapsed time for scanning and digitizing 11 cross-sectional images across a human eyeball is four seconds. During in vitro tests this system measured ocular volumes with a mean coefficient of variation of 2.8%. Accurate estimates of volume were obtained with measurements between 0.01 and 0.25 ml. This method of scanning is repeatable and reliable, and thus may have great potential for use in the diagnosis and treatment of intraocular tumors.—Michael A. Kass

*Department of Ophthalmology, University Hospital, Nørrebrogade 55, DK-8000 Århus C, Denmark.

Superior oblique palsy: Results of surgery in 443 cases. Maruo, T.*, Iwashige, H., Akatsu, S., Ishida, T., Tokutomi, M., Ikebukuro, N., Hayashi, T., and Kubota, N.: Binocular Vis. Quart. 6:143, 1991.

CONGENITAL SUPERIOR OBLIQUE MUSCLE PALSY, ACQUIRED SUPERIOR OBLIQUE MUSCLE PALSY, SURGICAL TREATMENT

The records of 443 patients with superior oblique muscle palsy treated with an operation were reviewed. In congenital superior oblique muscle palsy, the goal of treatment was to correct abnormal head position and vertical deviation. If the vertical deviation was small, the inferior oblique muscle was overacting, a myectomy of the inferior oblique muscle was performed. If the vertical deviation was large, a recession of the superior rectus muscle was also performed. If the inferior oblique muscle was not overacting, a recession of the superior rectus muscle was the initial procedure. In acquired superior oblique muscle palsy, the goal of treatment was to relieve cyclovertical diplopia. If there was substantial cyclodeviation, a Harada-Ito procedure was performed. If there was a substantial vertical deviation as well, a recession of the superior rectus muscle was also performed. If the cyclodeviation was minor, a recession of the contralateral inferior rectus muscle was performed. Using these guidelines, 73% of the patients with congenital palsy and 67% of the patients with acquired palsy were treated successfully. Additionally, 14% of the patients with the congenital palsy and 19% of the patients with acquired palsy were improved by an operation. In patients with a postoperative overcorrection, a masked bilateral superior oblique muscle palsy was often observed.—Michael A. Kass

*Department of Ophthalmology, Teikyo University School of Medicine, 11-1, Kaga, 2 Chome, Itabashi-Ku, Tokyo 173, Japan.

Retinal circulation times in diabetes mellitus type 1. Bertram, B.*, Wolf, S., Fiehofer, S., Schulte, K., Arend, O., and Reim, M.: Br. J. Ophthalmol. 75:462, 1991.

DIABETES MELLITUS, RETINAL ARTERIOVENOUS PASSAGE TIME

Video fluorescein angiography was performed in 124 patients with juvenile-onset diabetes mellitus. The arm-to-retina time and the retinal arteriovenous passage time were measured by means of an image analysis system that quantifies the retinal microcirculation. Glucose metabolism was assessed by the blood level of hemoglobin A1c. The arm-to-retina time was similar in patients with type 1 diabetes and in healthy individuals. However, the arteriovenous passage time was markedly longer in patients with diabetes (mean, 2.35 ± 0.87 seconds) than in healthy individuals (1.45 ± 0.40 seconds). The patients with the most severe diabetic retinopathy had the most marked change in arteriovenous passage time. Patients with diabetes with good control (hemoglobin A1c $\leq$ 8.0 g/dl) had shorter arteriovenous passage times than did patients with diabetes with poor glycemic control (hemoglobin A1c $>$ 9.5 g/dl). Patients with diabetes for five or more years had longer arteriovenous passage times than did patients in whom the diabetes was more recently diagnosed.—Michael A. Kass

*Augenklinik der RWTH Aachen, Pauwelsstrasse 30, 5100 Aachen, Germany.

Corrections

In the Letter to The Journal, "Differential intraocular pressure in restrictive strabismus," by M. Muñoz and H. Capó (Am. J. Ophthalmol. 112:352, September 1991), Figures 1 and 2 were inadvertently transposed.

In the article, "Cytomegalovirus retinopathy as the initial manifestation of the acquired immunodeficiency syndrome," by R. F. Sison, G. N. Holland, L. J. MacArthur, N. C. Wheeler, and M. S. Gottlieb (Am. J. Ophthalmol. 112:243, September 1991), the top of page 247, right column, should be "Pr($C/\bar{A}$)," not "Pr(C/A)." In line 15 of the same column, the probability should be "0.45%," not "45%."

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Ophthalmological Society of Northern Greece: 25th Panhellenic Ophthalmological Congress

The Ophthalmological Society of Northern Greece will hold the 25th Panhellenic Ophthalmological Congress, focusing on laser application in ophthalmology, June 4–7, 1992, in Halkidiki, Greece. For more information, write the Secretariat, University Eye Clinic, AHEPA Hospital, P.O. Box 10497, Thessaloniki, Greece; fax 031-209401.

Bascom Palmer Eye Institute: Cornea and External Disease 1992

The Bascom Palmer Eye Institute will offer a course, Cornea and External Disease, Jan. 17 and 18, 1992, at the University of Miami School of Medicine. For more information, write Continuing Education in Ophthalmology, P.O. Box 015869, Miami, FL 33101; telephone (305) 326-6099.

Stanford University Medical Center: The Management of Glaucoma

The Department of Ophthalmology at Stanford University Medical Center will offer a course, The Management of Glaucoma, Feb. 1, 1992. For additional information, write Continuing Education Programs, Dept. of Ophthalmology, A-157, Stanford University Medical Center, Stanford, CA 94305-5308; telephone (415) 725-7269.

Wilmer Ophthalmological Institute: 4th Annual Current Concepts in Ophthalmology

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor the 4th Annual Current Concepts in Ophthalmology plus Hands-On Excimer Laser and Phacoemulsification Wet Labs Dec. 12–14, 1991, in Baltimore, Maryland. For further information, write Program Coordinator, Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 20, Baltimore, MD 21205-2195; telephone (301) 955-2959.

Manhattan Eye, Ear & Throat Hospital: Lasers in Ophthalmology

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a Lasers in Ophthalmology course Jan. 10 and 11, 1992, in New York City. For additional information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

LuEsther T. Mertz Vitreous-Retina-Macula Lecture: Manhattan Eye, Ear & Throat Hospital

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will sponsor the LuEsther T. Mertz Vitreous-Retina-Macula Lecture in New York City on Jan. 21, 1992. The guest lecturer will be Daniel Finkelstein. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Nassau Surgical Society: Ophthalmic Plastic Surgery—21st Century Renaissance

The Nassau Medical Center will sponsor a course, Ophthalmic Plastic Surgery: 21st Century Renaissance, Dec. 11, 1991, at the Nassau Medical Center. For more information, write Francine Leinhardt, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200 ext. 2776; fax (212) 832-9126.

Hawaiian Eye Foundation: 13th Annual Royal Hawaiian Eye Meeting

The Hawaiian Eye Foundation will hold its 13th Annual Royal Hawaiian Eye Meeting Jan. 18–24, 1992, at the Grand Hyatt Wailea on Maui. For further information, write Hawaiian Eye Foundation, c/o Mary Charles & Associates, 2334 S. King St., Ste. 205, Honolulu, HI 96826; telephone (808) 942-9655.

Dallas Academy of Ophthalmology: New Officers

The Dallas Academy of Ophthalmology, founded in 1923, has announced new executive officers for 1991–1992: Craig D. Smith, president; William L. Hutton, vice president and public education chairman; Thomas P. Hawk, secretary-treasurer; and Rand Spencer, program chairman.

Pan-American Association of Ophthalmology: New Officers

Robert C. Drews of Clayton, Missouri, will succeed Enrique Malbran as president of the Pan-American Association of Ophthalmology (PAAO). Francisco Contreras of Lima, Peru, was named president-elect; and Alice McPherson of Houston, Texas, was named vice-president; Juan Verdaguer of Santiago, Chile, will serve as executive director. Secretary-treasurer for the English language will be Paul Lichter of Ann Arbor, Michigan; Francisco Martinez Castro of Mexico City, Mexico, will be secretary-treasurer for the Spanish language; and Rubens Belfort, Jr. of Sao Paulo, Brazil, will be secretary-treasurer for the Portuguese language.

Fight for Sight: Scientific Research Awards

Mildred Weisenfeld, founder and executive director of Fight for Sight, Inc., and James Wright, president of the National Society to Prevent Blindness, announce the scientific research awards approved for funding during the year 1991–1992.

The research awards program is administered in cooperation with the Association for Research and Vision and Ophthalmology; Henry F. Edelhauser is Association for Research in Vision and Ophthalmology director of scientific review. The scientific peer review of applications was conducted with volunteer support from the Association for Research in Vision and Ophthalmology members Scott Basinger, Jules Baum, Roger Beuerman, Joseph Behsarse, Gary Conrad, Cheryl Craft, Donald Doughman, Edmund Dunkel, Jay Enoch, Jorge Fishbarg, Douglas Gaasterland, Daniel Green, Robert Hendricks, Bret Hughes, Douglas Johnson, Harry Maisel, Robert Marc, John Nickerson, William O'Brien, Christopher Paterson, W. Gerald Robison, Stephen Sinclair, Paul Sternberg, Gary Trick, Ramesh Tripathi, George Williams, Rocky Young, and J. Samuel Zigler.

The Research Advisory Board, chaired by Arthur Silverstein, recommends policy concerning the awards program. Board members include Arthur Neufeld, Robert Nussenblatt, Steven Podos, Harris Ripps, and Melvin Rubin.

Grants-in-Aid

Thomas J. Byers, Ph. D., Dept. of Molecular Genetics, Ohio State University, Columbus, OH. Ribosomal RNA and DNA Sequence Discrepancies in Acanthamoeba. $11,000.

Mark H. Criswell, Ph.D., Dept. of Cell Biology and Anatomy, University of Health Sciences, The Chicago Medical School, North Chicago, IL. Rabbit Starburst Amacrine Cells: A Study to Correlate Structure with Function. $11,000.

Elizabeth A. Debski, Ph.D., Dept. of Biological Sciences, University of Kentucky, Lexington, KY. Somatostatin, VIP and Visual Map Formation in Rana Pipiens. $9,500.

Michael A. Edwards, Ph.D., Dept. of Developmental Neurobiology, Eunice Kennedy Shriver Center, Waltham, MA. Defective Optic Axon Outgrowth in an Anophthalmic Mutant Mouse: Analysis Using Chimeras and Immunocytochemistry. $11,000.

Felix I. Ifeanyi, Ph.D., Division of Biology, Kansas State University, Manhattan, KS. Identification of Lens Membrane Recognition Site(s) of Alpha Crystallin. $11,000.

Terence P. Ma, Ph.D., Dept. of Anatomy, University of Mississippi Medical Center, Jackson, MS. Functional Relationship of the Incertotectal Projection in the Macaque. $11,000.

Steven A. Madreperla, Ph.D., M.D., Dept. of Ophthalmology, Johns Hopkins University, Baltimore, MD. Replacement of the RB Gene in Retinoblastoma Cells: Effects on Tumorigenesis. $11,000. Awarded in Tribute to Bob Hope.

Helen McIntosh, Ph.D., Dept. of Biochemistry & Molecular Biophysics, Washington University, St. Louis, MO. Localization and Biochemical Characterization of Adenosine A2 Receptors in Bovine Rod Outer Segments. $11,000.

Jay F. Muller, Ph.D., Dept. of Ophthalmology, Washington University, St. Louis, MO. Synaptic Connectivity of Transplanted Photoreceptors. $7,000.

Ramesh C. Nayak, Ph.D., Research Division, Joslin Diabetes Center, Boston, MA. Characterization of Retinal Microvascular Pericyte Antigens Defined by Circulating Anti-Pericyte Antibodies in Retinopathic Diabetics. $10,000. (Awarded in Memory of Mary E. and Alexander P. Hirsch.)

Ann M. Repka Ph.D. Dept. of Ophthalmology, Johns Hopkins University, Baltimore, MD. Investigation into the Factors Controlling the Determination of Retinal Precursor Cell Phenotype. $11,000.

Bratin K. Saha, Ph.D., Dept. of Pathology, Washington University, St. Louis, MO. Development of Novel RFLP Probes for Carrier Detection and Prenatal Diagnosis of X-Linked Retinitis Pigmentosa. $11,000. (Awarded in Memory of Silas Adelsheim.)

Ursula M. Schmidt, M.D., Dept. of Dermatology, Massachusetts General Hospital, Boston, MA. Carrier Systems for Improved Selectivity of Photodynamic Therapy in Vascular Occlusion. $11,000.

Marc D. Servetnick, Ph.D., Dept. of Biology, The University of Virginia, Charlottesville, VA. Regulation of Competence for Lens Induction in Xenopus Development. $11,000.

Carol B. Toris, Ph.D., Dept. of Ophthalmology, University of Nebraska, Omaha, NE. Mechanism of Action of Acetazolamide Decreasing Intraocular Pressure. $10,000.

Janey L. Wiggs, M.D., Ph.D., Dept. of Ophthalmology, Massachusetts Eye & Ear Infirmary, Boston, MA. Genetic Linkage Study of Autosomal Dominant Juvenile Glaucoma. $11,000.

Steven E. Wilson, M.D., Dept. of Ophthalmology, University of Texas, Dallas, TX. Growth Factor and Growth Factor Receptor mRNA Expression in Corneal Epithelium. $10,000.

Tanweer S. Zaidi, Ph.D., Dept. of Ophthalmology, Tufts University, Boston, MA. The Role of Ocular Mucus in Providing Protection from Pseudomonal Corneal Infection. $11,000.

Postdoctoral Research Fellowships

Michael L. Cooper, Ph.D., M.D., Dept. of Ophthalmology, Mt. Sinai Medical School, New York, NY (Steven M. Podos, M.D., Sponsor). Ocular Blood Flow in Glaucoma. $14,000. (Awarded in Memory of Mary E. and Alexander P. Hirsch.)

Mordechai Goldenfeld, M.D., Dept. of Ophthalmology, Northwestern University, Chicago, IL (Jon M. Ruderman, M.D., Sponsor). Optic Disc Analysis Using Digitized Photography and Flicker Analysis. $14,000.

Karen L. Kittredge, M.D., Dept. of Ophthalmology, University of Virginia Charlottesville, VA (Frederico Gonzalez-Fernandez, Ph.D., Sponsor). Molecular & Functional Analysis of Interphotoreceptor Retinol-Binding Protein (RBP) in Xenopus Laevis. $14,000.

Ioannis Koutalos, Ph.D., Dept. of Neuroscience, The Johns Hopkins University, Baltimore, MD (King-Wai YAU, Ph.D., Sponsor). Phototransduction in Retinal Cone Cells. $14,000. (Awarded in Memory of Mary E. and Alexander P. Hirsch.)

Ilona Kovacs, Ph.D., Dept. of Psychology, Rutgers University, New Brunswick, NJ (Bela Julesz, Ph.D., Sponsor). Learning Effects & Interaction of Different Visual Attributes in Stereoscopic Depth Perception. $13,000. (Awarded in Memory of Dr. Hermann M. and Gladys Burian.)

Elsa M. Raskin, M.D., Dept. of Ophthalmology, New York Eye & Ear Infirmary, New York, NY (Mark G. Speaker, M.D., Ph.D., Sponsor). Molecular Biology of Staphylococci Causing Postoperative Endophthalmitis. $14,000. Awarded in Tribute to Bob Hope.

Ellie E. Samadani, M.D., Dept. of Ophthalmology, Wayne State University Detroit, MI (Robert N. Frank, M.D., Sponsor). Studies of the Physiology and Pathophysiology of the Retinal Capillaries. $14,000. Awarded in Honor of Dr. Charles A. Perera.

Elcio H. Sato, M.D., Department of Immunology, Eye Research Institute, Boston, MA (David A. Sullivan, Ph.D., Sponsor). Influence of Hormone Therapy in Sjogren's Syndrome in Lacrimal Gland. $2,000 (extension of 1990-91 postdoctoral fellowship).

Andrew W. Taylor, Ph.D., Dept. of Microbiology/Immunology, University of Miami, Miami, FL (Scott W. Cousins, M.D., Sponsor). Immunosuppressive Activity of a-MSH in Aqueous Humor. $14,000.

Lifang Tien, M.D., Ph.D., Dept. of Ophthalmology, Baylor College of Medicine, Houston, TX (Joe G. Hollyfield, Ph.D., Sponsor). The Composition and Cellular Origin of the WGA-Binding Domain of the IPM in Human Retina. $14,000.

Student Fellowships

Jameel Almed, Dept. of Biomedical Engineering, Northwestern University, Evanston, IL (Robert A. Linsenmeier, Ph.D., Sponsor). Regional Variations in Oxygen Supply and Photoreceptor Oxygen Consumption in the Cat Retina. $1,500. (Awarded in Memory of Herman Shane.)

Claire L. Bautista, Dept. of Biology, University of South Florida, Tampa, FL (Alvin F. Wells, Ph.D., Sponsor). The Role of Borrelia Antigens in Ocular Inflammation. $1,500. Awarded in Honor of Neil and Donna Weisman.

Anastasia V. Deliganis, Dept. of Biological Structures, University of Washington, Seattle, WA (Thomas A. Reh, Ph.D., Sponsor). Basic Fibroblast Growth Factor Receptor Expression During Retinal Regeneration. $1,500. Supported by the Albert G. and Herman B. Mosler Memorial Fund.

Karen V. Gonzalez, Dept. of Biochemistry, Kansas State University, Manhattan, KS (Dolores J. Takemoto, Ph.D., Sponsor). The Role of the Na^+, K^+-ATPase in Diabetic Retinopathy and Cataract Formation. $1,250. Supported by a grant from the Radio and Television Square Club.

Terry Kim, Dept. of Ophthalmology, Duke University, Durham, NC (Gordon K. Klintworth, M.D., Ph.D., Sponsor). Investigation of the Effects of Vasoconstriction on Corneal Neovascularization Using an In Vivo Model. $1,500. (Awarded in Memory of Norma Cohen.)

E. Anders Kolb, Dept. of Neuroscience, University of Pennsylvania, Philadelphia, PA (David J. Calkins, Ph.D., Sponsor). The Microcircuitry of the Midget Ganglion Cell Pathway in Macaca. $1,500.

Norman L. Lehman Jr., Dept. of Ophthalmology, University of California, San Francisco, CA (Richard B. Crook, Ph.D., Sponsor). Na^+, K^+, $C1^-$ Cotransport in Postnatal Human Non-Pigmented Ciliary Epithelial Cells. $1,500. Awarded in Honor of Elsie K. Sloate.

Bettye D. Ridley, Dept. of Biological Sciences, University of Kentucky Lexington, KY (Philip H. Bonner, Ph.D., Sponsor). The Development of Extraocular Muscle in Chick Embryos. $1,500. (Awarded in Memory of Selma Rabin.)

Keith Rosol, Dept. of Anatomy and Cell Biology, Wayne State University, Detroit, MI (Linda D. Hazlett, Ph.D., Sponsor). Localization of Putative Host Receptors for P. Aeruginosa in the Mouse Eye. $1,500. (Awarded in Memory of Selma Rabin.)

Isaac E. Silverman, Dept. of Psychology, Princeton University, Princeton, NJ (Charles G. Gross, Ph.D., Sponsor). Visual Imagery in the Macaque: Lesion & Electrophysiological Investigations. $1,500.

Catherine D. Thaler, Dept. of Biology, University of California, Riverside, CA (Leah T. Haimo, Ph.D, Sponsor). Regulation of Organelle Transport in RPE. $1,500. Supported by the James Thurber Memorial Fund.

Jingjing Ye, Dept. of Physiology, New York University, New York, NY (Jose A. Zadunaisky, M.D., Ph.D., Sponsor). Membrane Transport and H_2O_2 Oxidating in Lens Epithelial and Fiber Cell Membrane Vesicles. $1,500. (Supported by a grant from Canon, U.S.A., Inc.)

An additional grant-in-aid was funded by Fight for Sight, Inc., to J. Arch McNamara, M.D., Dept. of Ophthalmology, Wills Eye Hospital, Philadelphia, PA. Laser Photocoagulation for Stage 3+ Retinopathy of Prematurity. $27,495. This application was reviewed independently by authorities in pediatric ophthalmology and was funded with support from the Fight for Sight of Greater Philadelphia.

Personal

Morton E. Smith

Morton E. Smith, professor of ophthalmology and pathology at Washington University School of Medicine, St. Louis, Missouri, has been promoted to Associate Dean for Postgraduate Education. In addition to his new duties as associate dean, Dr. Smith will continue as Director of Ophthalmic Pathology and course director in ophthalmology for medical students.

Results and Complications in Treated Retinal Breaks

William E. Smiddy, M.D., Harry W. Flynn, Jr., M.D., Don H. Nicholson, M.D.,
John G. Clarkson, M.D., J. Donald M. Gass, M.D., Kal R. Olsen, M.D.,
and William Feuer, M.S.

One hundred sixty-four patients (171 eyes) were treated for retinal breaks and the treatment outcomes were studied. One hundred two eyes were acutely symptomatic, 22 eyes were chronically symptomatic, and 47 eyes were asymptomatic. The reasons for further treatment in 38 of the 171 eyes (22%) included the following: (1) inadequate closure of the original break without detachment in eight eyes (5%), (2) new breaks without detachment in 15 eyes (9%), (3) an operation for retinal detachment caused by the original break in seven eyes (4%), or (4) retinal detachment caused by a new break in eight eyes (5%). Failure rates of treatment among acutely symptomatic, chronically symptomatic, and asymptomatic subgroups were not statistically significant. The risk of treatment failure was higher for aphakic and pseudophakic eyes, and in eyes with peripheral retinal abnormalities in the fellow eye. Among 38 patients with failed treatments, 20 (52%) returned for further examination within one month of initial treatment, whereas eight of the 38 patients with failed treatments (21%) returned six months or more after initial treatment. Peripheral retinal abnormalities were recognized initially in 65 of the 171 fellow eyes (38%) and subsequently developed in nine of the fellow eyes (5%) during the follow-up interval. Further treatment is often necessary after initial treatment of peripheral retinal breaks, emphasizing the need for careful long-term follow-up care.

DIATHERMY,[1,2] photocoagulation,[3-6] and retinocryopexy[5-7] have been effective prophylaxes against retinal detachment for retinal tears. Although round holes are etiologically associated with up to 30% of retinal detachments,[8,9] asymptomatic round holes have been recognized to be nonprogressive[10-15] and are not usually treated.[16-18] Many factors now form the basis for deciding which retinal breaks have a high enough risk of progressing to retinal detachment to merit treatment. Most studies have evaluated the treatment outcomes after prophylactic treatment of retinal breaks before relative risk factors were identified, or consisted of a high proportion of low-risk patients with asymptomatic eyes.[3-7,16,17,19-23]

The purpose of our study was to evaluate the frequency of failed treatment of retinal breaks as measured by the rates of retreatment, new break formation, and retinal detachment requiring a retinal reattachment and to determine factors associated with higher failure rates.

Patients and Methods

Patients were included in this study if they were treated for retinal breaks, and at least three months of follow-up information was available, unless treatment failed. Patients with untreated retinal breaks were not included. Patients were identified by two means. First, the procedure log books for laser treatment and cryotherapy were reviewed and eyes were identified. Second, a list of all patients who underwent retinocryopexy or laser photocoagulation was obtained from the designated treatment codes in the billing department. Only patients treated by the full-time retina faculty of our institution between July 1, 1984, and December 31, 1989, were included. Of 231 eyes identified, 20 were excluded because a chart could not be located by the medical records department and 40 eyes were excluded because of inadequate follow-up information.

The charts were reviewed for the following

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From the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida.

Reprint requests to William E. Smiddy, M.D., P.O. Box 016880, Miami, FL 33101.

preoperative information: (1) age, (2) gender, (3) date of treatment, (4) presence and form of symptoms, (5) duration of symptoms, and (6) visual acuity. All full-thickness retinal defects were referred to as retinal breaks; acute, traction-induced breaks were referred to as retinal tears; and chronic, atrophic, or traction-free breaks were referred to as retinal holes. Eyes with symptoms 30 days or more in duration were defined as chronically symptomatic. Eyes with new symptoms (photopsia, floaters, decreased visual acuity) within 30 days before treatment were defined as acutely symptomatic.

The following clinical features were recorded: (1) type of retinal break (round, round with free operculum, and horseshoe-shaped); (2) anterior-posterior break location; (3) meridional location of break; (4) number of breaks; (5) presence and severity of vitreous hemorrhage; (6) presence and extent of subretinal fluid; (7) lens status; (8) visual acuity with best spectacle refraction; (9) refractive status of the eye; (10) treatment method; and (11) status of the fellow eye with regard to visual acuity and peripheral retinal abnormalities, such as retinal breaks, lattice degeneration, or detachment (treated and untreated).

Meridional locations were defined as follows: superior quadrant from the 10:30 meridian up to but not including the 1:30 meridian, inferior quadrant from the 4:30 meridian up to but not including the 7:30 meridian, and the nasal and temporal quadrants were in between.

A mild amount of subretinal fluid was defined as the diameter of an area less than 2 disk diameters of surrounding subretinal fluid, whereas a moderate amount exceeded this definition.

A minimal amount of vitreous hemorrhage was defined as hemorrhage associated with the break on the internal retinal surface, but not apparent by clinical examination of the vitreous cavity. Mild vitreous hemorrhage was defined by the minimal amount of vitreous red blood cells detectable using slit-lamp biomicroscopy. A moderate amount of vitreous hemorrhage was defined as enough vitreous hemorrhage to cause a subjective decrease in visual acuity.

The refractive status was recorded as the nearest whole number of the dioptric power. The refractive status before the cataract operation was recorded from the chart or as a best estimate on the basis of the status of the fellow eye in the 25 patients whose eyes were aphakic or pseudophakic.

The most recent follow-up examination features were obtained from the medical records of the treating physician in 158 eyes and from the referring physician in 15 eyes. A determination for each of the following end point variables was obtained: (1) further retinopexy treatment, (2) subsequent retinal detachment operation, (3) development of a new break, (4) epiretinal membrane formation, (5) visual acuity, (6) new break or treatment in the fellow eye, and (7) date of final follow-up examination. Patients without the first three of these variables over the minimal three-month follow-up interval were considered to have been successfully treated.

Computer-assisted tabulation and statistical evaluations were performed to determine the greatest risk features for these end point variables.

Results

Patient and retinal break characteristics—One hundred seventy-one eyes of 164 patients were involved in this study. One hundred eight of the 171 eyes (63%) were from male patients (102 of 164 patients were male) and 63 of the 171 eyes (37%) were from female patients (62 of 164 patients were female). The average age was 59.0 years and ranged from 14 to 84 years. Forty-seven eyes (27%) were asymptomatic; 22 eyes (13%) were chronically symptomatic; and 102 eyes (60%) were acutely symptomatic. The 124 eyes with symptomatic retinal breaks included photopsia in 17 eyes (14%), floaters in 48 eyes (39%), and decreased visual acuity in 25 eyes (20%).

The retinal break was anterior to the equator in 163 eyes (95%). The break was in the superior quadrant in 102 eyes (60%), was in the inferior quadrant in 20 eyes (12%), and was in the nasal or temporal quadrant in 49 eyes (29%). Only one retinal break was detected in 123 eyes (71%). In eyes with multiple breaks, all breaks were treated except in one eye in which a symptomatic horseshoe break was treated, but in which a round hole was also observed.

The acutely symptomatic group of patients had a higher proportion of eyes with operculated breaks, without subretinal fluid, and with vitreous hemorrhage (Table 1). The asymptomatic group of patients had a higher proportion of peripheral retinal abnormalities, previous

TABLE 1
DIFFERENCES BETWEEN ACUTELY SYMPTOMATIC GROUP AND CHRONIC OR ASYMPTOMATIC GROUP*

	NO. OF ACUTELY SYMPTOMATIC EYES (%) N = 102	NO. OF CHRONICALLY SYMPTOMATIC EYES (%) N = 22	NO. OF ASYMPTOMATIC EYES (%) N = 47
Hole description (P = .022)			
Round	9 (9)	3 (14)	12 (26)
Horseshoe-shaped	77 (75)	18 (82)	33 (70)
Operculated	16 (16)	1 (4)	2 (4)
Subretinal fluid (P = .0004)			
None	76 (74)	9 (41)	30 (64)
Minimal	18 (18)	10 (45)	4 (9)
Moderate	10 (10)	3 (14)	13 (28)
Vitreous hemorrhage (P = .0001)			
None	64 (63)	19 (86)	46 (98)
Local	3 (3)	0 (0)	1 (2)
Minimal	19 (18)	2 (9)	0 (0)
Moderate	16 (16)	1 (5)	0 (0)
Status of fellow eye (P = .0003)			
Normal periphery	74 (73)	14 (64)	18 (38)
Peripheral retinal breaks or lattice	28 (27)	8 (36)	29 (62)
Previous treatment of fellow eye (P = .001)			
Yes	23 (23)	7 (32)	25 (53)
No	79 (77)	15 (68)	22 (47)
Previous scleral buckling procedure in fellow eye (P = .004)			
Yes	17 (17)	2 (9)	18 (38)
No	85 (83)	20 (91)	29 (62)

*P values in the statistical analysis were calculated using Chi-squared testing.

retinal detachment operations, and previous laser treatment or retinocryopexy of the fellow eye.

The adjusted, phakic refractive status of the treated eye measured 6 or more diopters of myopia in 31 of the 171 eyes (18%), −5 to −1 diopters in 46 eyes (27%), plano in 44 eyes (25%), and +1 to +4 in 50 eyes (29%). One hundred forty-six eyes (85%) were phakic; 11 (6%) were aphakic; and 14 (8%) were pseudophakic. In 11 eyes, the intraocular lens was a posterior chamber lens and in three eyes, the intraocular lens was an anterior chamber lens. The posterior capsule had been opened in three of the 11 eyes with posterior chamber intraocular lenses.

The peripheral retina of the fellow eye at the time of treatment of the study eye was normal in 106 of the 171 eyes (62%), but contained peripheral retinal abnormalities in 65 (38%). The fellow eye had been previously treated in 55 patients, including a scleral buckling procedure in 17 of the 102 (17%) acutely symptomatic eyes and in 20 of the 22 (90%) chronically symptomatic eyes. Forty-six of the 55 previously treated eyes had been treated elsewhere.

Treatment information—Laser treatment alone was used in 92 eyes (54%), retinocryopexy alone was used in 58 eyes (34%), and both modalities were used in 21 eyes (12%).

The reasons given for treatment of the 47 asymptomatic eyes included the following: (1) previous retinal detachment in the fellow eye (15 eyes); (2) increasing subretinal fluid (14 eyes); (3) treatment of similar, though usually symptomatic, abnormalities in the fellow eye (five eyes); (4) large size of the retinal break (four eyes); (5) treatment immediately preceding cataract extraction (three eyes); (6) severe myopia (two eyes); (7) horseshoe-shaped break after acute blunt trauma (one eye); (8) horseshoe-shaped break in aphakic eye (one eye); and (9) no stated reason (two eyes). Many patients in this study had multiple stated reasons for treatment. For example, in one patient an asymptomatic break was treated because of poor visual acuity after retinal detachment in the fellow eye and an upcoming cataract operation. Despite the chronicity, the presence of symptoms was the main reason for treatment of the 22 chronically symptomatic eyes.

Treatment outcome—The follow-up interval for eyes that did not undergo retreatment ranged from three months to 61 months with an average of 20 months. There was at least one year of follow-up in 94 eyes (55%).

Further treatment performed in 38 eyes (22%) during the follow-up interval included a scleral buckling procedure in 15 eyes (9%), retinocryopexy only in ten eyes (4%), laser treatment only in 11 eyes (6%), and retinocryopexy and laser treatment in two eyes (3%). A new retinal break was noted in 24 eyes (14%) and was treated in 23 eyes. The new break occurred within a clock hour of the original tear in eight eyes (35%) that developed new breaks. The original retinal break underwent further laser or retinocryopexy treatment in eight eyes because the treating physician judged it to be not adequately closed with initial treatment. Retinal detachment requiring scleral buckling procedure was associated with a new retinal break in eight eyes and was associated with the original break in seven eyes. Although 14 of 15 eyes with retinal detachment were successfully reattached, the macula had become detached in ten eyes. The Kaplan-Meier two-year cumulative proportions for treatment failure were tabulated for further treatment (38 eyes for 25%), new break formation (24 eyes for 15.8%), and retinal detachment (15 eyes for 10%; Figure). Most treatment failures were apparent soon after initial treatment, but a substantial proportion did not become apparent until at least one month later. For example, 21 of 38 (55%) retreatments were within the first month, but 21% were after six months.

The 22 chronically symptomatic, 47 asymptomatic, and 102 acutely symptomatic eyes were analyzed separately (Table 2). The treatment failure rates in the acutely symptomatic group of patients were similar to those in the asymptomatic group and were as follows: further treatment, ten eyes, 21% failure rate vs 28 eyes, 27% failure rate; new breaks, six eyes, 13% failure rate vs 18 eyes, 21% failure rate; and clinical retinal detachment, 11 eyes, 11% failure rate vs four eyes, 9% failure rate. No treatments failed among the 22 chronically symptomatic eyes. However, these differences were only statistically significant for the end point of undergoing retreatment (P = .032). That is, the rate of development of new tears or clinical retinal detachment was not statistically significantly different between the three groups (P = .11 and P = .28, respectively).

The final spectacle-corrected visual acuity was ≥ 20/50 in 152 of all 171 eyes (89%), but in only 27 of the 38 eyes (71%) undergoing further treatment (Table 3). Reasons for visual acuity < 20/50 among retreated eyes included previous macular involvement by retinal detachment

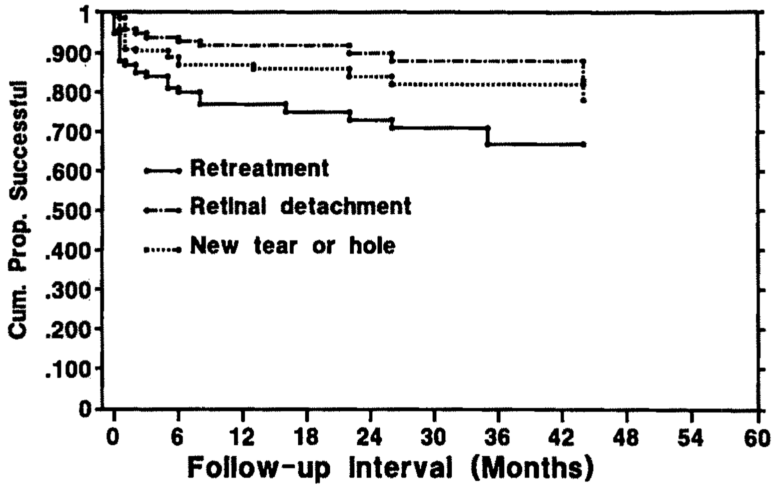

Figure (Smiddy and associates). Survival curves after treatment of retinal breaks as measured by the outcome of retreatment, retinal detachment requiring scleral buckling procedure, and development of new retinal breaks.

TABLE 2
RATES OF FURTHER TREATMENT, NEW BREAK FORMATION, AND RETINAL DETACHMENT

	NO. OF ACUTELY SYMPTOMATIC EYES (%) N = 102	NO. OF CHRONICALLY SYMPTOMATIC EYES (%) N = 22	NO. OF ASYMPTOMATIC EYES (%) N = 47
Retreated (%)	28 (27)	0 (0)	10 (21)
No. retreated within one month (%)	18 (64)	0 (0)	3 (30)
Cumulative Kaplan-Meier percentage with retreatment at			
3 months	20	0	11
1 year	24	0	20
2 years	30	0	24
	Differences Among Groups, P = .032*		
No. developing new breaks (%)	18 (18)	0 (0)	6 (13)
Cumulative Kaplan-Meier percentage developing new breaks at			
3 months	13	0	6
1 year	16	0	12
2 years	21	0	12
	Differences Among Groups, P = .11		
No. developing clinical retinal detachment (%)	11 (11)	0 (0)	4 (9)
Cumulative Kaplan-Meier percentage undergoing retinal rettachment at			
3 months	8	0	5
1 year	10	0	8
2 years	13	0	8
	Differences Among Groups, P = .28		

*Mantel-Cox statistic.

(nine eyes), albinism (one eye), and traumatic retinopathy (one eye). For eyes not undergoing retreatment, macular degeneration (two eyes), corneal edema (two eyes), cataract, pseudophakic cystoid macular edema, posterior capsule opacity, and myopic macular degeneration (one eye each) caused a decrease in visual acuity to < 20/50.

TABLE 3
CORRECTED VISUAL ACUITY BEFORE AND AFTER TREATMENT OF RETINAL BREAKS

VISUAL ACUITY	NO. OF EYES BEFORE TREATMENT (%)	NO. OF EYES AFTER TREATMENT (%)	NO. OF EYES RETREATED (%)
20/15–20/50	144 (84)	152 (89)	27 (71)
20/60–20/200	20 (12)	9 (5)	4 (11)
< 20/200	7 (4)	10 (6)	7 (18)
Total (%)	171 (100)	171 (100)	38 (22)

An epiretinal membrane was observed after treatment in nine eyes, but was severe enough to require an operation in only one eye.

Risk analysis for treatment failure—A multivariate analysis of risk factors was performed using Cox proportional hazards model[24] regression for retreatment, new retinal breaks, and retinal detachment requiring an operation for the overall group (the three measures of outcome; Table 4) and for the acutely symptomatic and asymptomatic subgroups (Table 5). The low number of eyes in the chronically symptomatic group precluded this analysis in that subgroup.

TABLE 4
RESULTS OF MULTIVARIATE RISK FACTOR ANALYSIS FOR TREATMENT FAILURE IN GROUP OF 171 EYES WITH TREATED RETINAL BREAKS

RISK FACTOR	RATIO OF POOR OUTCOME RATE IN RISK GROUP TO THAT IN REFERENCE GROUP (P VALUE)*	95% CONFIDENCE INTERVAL ON RATE RATIO
Outcome = Retreatment		
Aphakic or pseudophakic	5.7 (P = .0001)	2.8 to 11.7
Acute symptoms	3.2 (P = .002)	1.5 to 6.7
Scleral buckle procedure in fellow eye	2.5 (P = .013)	1.3 to 5.0
Male	2.4 (P = .019)	1.1 to 5.0
Outcome = New Retinal Break		
Aphakic or pseudophakic	5.2 (P = .002)	2.0 to 13.3
Male	4.1 (P = .005)	1.3 to 12.5
Acute symptoms	3.2 (P = .008)	1.3 to 8.2
Peripheral or retinal abnormalities in fellow eye	2.7 (P = .021)	1.1 to 6.3
Outcome = Retinal Detachment (Requiring Scleral Buckle Procedure)		
Aphakic or pseudophakic	5.4 (P = .004)	1.9 to 15.5

*P values in the statistical analysis were calculated using Cox proportional hazards regression model.

Pseudophakia or aphakia was a statistically significant risk factor associated with failure for all outcome measures for the overall group (Table 4). For the overall group, acute symptoms and male gender were risk factors for failure as measured by rates of retreatment and new break formation, but not for the outcome of retinal detachment requiring scleral buckling procedures. A scleral buckle procedure in the fellow eye was a risk factor for retreatment and peripheral retinal abnormalities in the fellow eye was a risk factor for new retinal break formation.

In the subgroup analysis, aphakia or pseudophakia was usually a risk factor for failure for all outcome measures and all subgroups. Male gender was a risk factor for retreatment and new break formation in the acutely symptomatic group, whereas younger age and the finding of peripheral retinal abnormalities were risk factors for retreatment in the asymptomatic group. History of scleral buckling procedure in the fellow eye was a retreatment risk factor in the acutely symptomatic group. Previous retinal break and nonround-hole configuration were risk factors for new retinal break formation in the acutely symptomatic group. The presence of subretinal fluid showed borderline significance in a univariate sense (P = .076), but lost statistical significance when other terms were included in the model.

Pseudophakia or aphakia was the only risk factor for retinal detachment requiring scleral buckling procedure. All three patients with posterior chamber intraocular lenses and an open posterior capsule subsequently developed retinal detachment from reopening of the originally treated break in each eye, compared to none of the eight with intact capsules and one of three with anterior chamber intraocular lenses. Lower preoperative visual acuity was correlated with failure in the univariate analysis (P = .050), but was not statistically significant in the multivariate analysis.

Factors that were not related to an increased or decreased tendency for retreatment, new breaks, or clinical retinal detachment included the following: age, initial treatment (laser treatment vs cryopexy), number of retinal breaks, location of retinal breaks (meridional or anterior to posterior), and the presence of vitreous hemorrhage. None of the variables was synergistic.

Discussion

This study demonstrated the following appreciable two-year cumulative rates after initial treatment of retinal breaks: 25% for further treatment (of old or new breaks or for retinal detachment), 15.8% for new break development, and 10% for clinical retinal detachment. The most surprising finding was that the two-year cumulative rates were similar for all subgroups (that is, acutely symptomatic, symptomatic, and chronically symptomatic). These results are in contrast to previously published studies of retinal break treatments, which

TABLE 5
RESULTS OF RISK FACTOR ANALYSIS FOR TREATMENT FAILURE IN ACUTELY SYMPTOMATIC VS ASYMPTOMATIC SUBGROUPS*

Outcome = Retreatment	
Acutely symptomatic group	
Aphakic or pseudophakic	P = .005
Gender (male)	P = .017
Scleral buckle in fellow eye	P = .092
Asymptomatic group	
Aphakic or pseudophakic	P = .0001
Age (younger)	P = .060
Peripheral retinal abnormalities	P = .0094
Outcome = New Retinal Break	
Acutely symptomatic group	
Aphakic or pseudophakic	P = .055
Previous retinal break	P = .058
Gender (male)	P = .036
Nonround hole	P = .031
Asymptomatic group	
Aphakic or pseudophakic	P = .089
Outcome = Retinal Detachment (Requiring Scleral Buckle Procedure)	
Acute symptomatic group	
Aphakic or pseudophakic	P = .078
Asymptomatic group	
Aphakic or pseudophakic	P = .014

*P values in the statistical analysis were calculated using Cox proportional hazards regression model.

found up to a 10% rate of new break formation and a 6% rate of retinal detachment in studies composed of 6% to 63% of eyes with asymptomatic breaks (Table 6).[4-7,19,20,25]

The 38% rate of preexisting peripheral retinal abnormalities in our study, such as retinal breaks, lattice degeneration, or detachment in the fellow eye, was similar to the rate in other studies, which ranged from 27% to 42%.[6,7,19,20] The 5% incidence of new break formation in the fellow eye in this study emphasizes the importance of careful follow-up examination of both eyes.

A study of the natural course of the condition showed that ten eyes with untreated, symptomatic breaks all progressed to retinal detachment within six weeks.[26] In our study, treatments failed usually within one month, but 21% failed six months or more after the original treatment. Others have also shown that secondary retinal breaks or retinal detachment develops in most eyes within a few months after prophylactic treatment, but a small proportion does not develop until the distant future.[5,6,20,25] A risk factor analysis in this study showed that aphakia or pseudophakia was consistently as-

TABLE 6
RESULTS OF PREVIOUS STUDIES OF TREATED PERIPHERAL RETINAL BREAKS

	NO. EYES	(%) BREAKS	(%) RETINAL DETACHMENT	(%) EPIRETINAL MEMBRANE
Robertson and Norton[19]	301	5.5	6.0	1
Combs and Welch[20]	177	7.3	4.5	2
Straatsma, Allen, and Christensen[4]	74	2.7	2.7	—
Chignell and Shilling[5]	231	—	5.0	—
Kanski and Daniel[6]	701	8.0	4.7	—
Morse and Scheie[7]	231	0	0	0
Goldberg and Boyer[25]	83	10.0	—	—
Our study	171	14.0	9.0	5

sociated with treatment failure for both acute and chronic eyes. Acute symptoms and previous peripheral retinal disease in the fellow eye were also important risk factors. Hence, long-term follow-up examinations and patient education for new symptoms are all important, especially in these higher-risk subgroups.

The location of 65% of new breaks away from the original site in our study was similar to that in a recent study,[20] but contrasts to earlier studies consisting mainly of treated asymptomatic eyes in which 54% to 67% of new breaks occurred near the previously treated area.[5,6,19,25]

The final visual acuity was generally good in our study, particularly among those eyes in which subsequent macula-involving retinal detachment was avoided. The 89% incidence of 20/50 or better final visual acuity is similar to the experience of Combs and Welch[20] and consistent with the 4% incidence of visual loss found after treatment in another study.[5]

The incidence of macular pucker after prophylactic treatment has usually been reported to be from 1% to 2%.[19,20] However, a prospective study found a 5% incidence of severe (Grade 3) macular pucker after retinal break treatment, but a 42% incidence when milder forms are counted.[27] Subtle, visually undetectable membranes may often be undiagnosed in retrospective studies, thereby frustrating meaningful comparison.

Acute symptomatic retinal breaks are now treated prophylactically by most vitreoretinal specialists, but controversy continues regarding the management of asymptomatic retinal breaks.[28] Compared to horseshoe breaks, round holes with or without lattice degeneration are an important, but less common cause of retinal detachment, occurring in 30% of patients with retinal detachment.[17,18] However, their high prevalence in the general population and stability in long-term studies of the natural course of the abnormality[12-14] suggest that most round holes do not require treatment. Consideration of various coexisting risk factors, such as retinal detachment in the fellow eye, aphakia, and myopia, may influence the decision to treat asymptomatic eyes. In our study, the chronic subgroup did have appreciable rates of retinal detachment, new breaks, and retreatment, but this study probably represented a sampling of high-risk eyes.

In one study of fellow eyes in patients with retinal detachment, detachment associated with asymptomatic, untreated breaks developed in 8.2% compared with 4.8% of prophylactically treated eyes.[21] Another study of asymptomatic patients with phakic fellow eyes of lattice-associated retinal detachment found that untreated eyes had a 5.1% incidence of developing a new break or retinal detachment compared to only 1.8% of those being treated prophylactically for lattice-associated retinal breaks.[22] However, prophylactic treatment did not reduce the risk of detachment in eyes with severe myopia or extensive lattice, nor did it eliminate the risk of retinal detachment caused by new retinal breaks occurring outside of the prophylactically treated area.

Aphakia or pseudophakia is another factor that may influence the decision to treat an asymptomatic break. Although appropriate control groups were lacking, two studies found the rate of retinal detachment in the fellow eyes of patients with aphakic retinal detachment to be reduced by prophylactic treatment of asymptomatic breaks.[21,23]

The rate of retinal break formation and retinal detachment is increased in severe myopia,[18] especially after cataract extraction.[29] However, because new abnormalities often develop in areas distant from the established abnormality, efficacy of prophylactic treatment of asymptomatic breaks in this subgroup is unproven.[30]

Thus, treatment of asymptomatic patients with retinal breaks remains controversial. However, it should be considered in nonphakic eyes with fellow-eye abnormality,[21,23] and in lattice-associated retinal detachments.[22]

New or recurrent abnormalities often develop after prophylactic treatment of retinal breaks and our conclusion is more common in aphakic or pseudophakic eyes, in eyes with peripheral abnormalities in the fellow eye, and in acutely symptomatic eyes. Although the abnormalities usually develop within the first few months, they may develop several months or years after initial treatment. Careful, long-term follow-up examinations and patient education are recommended for effective management and preservation of good visual acuity.

References

1. Schepens, C.: Subclinical retinal detachments. Arch. Ophthalmol. 47:593, 1952.
2. Colyear, B. H., and Pischel, D. K.: Clinical tears in the retina without detachment. Am. J. Ophthalmol. 41:773, 1956.
3. Meyer-Schwickerath, G.: Indications and limi-

tations of light coagulation of the retina. Trans. Am. Acad. Ophthalmol. 63:725, 1959.

4. Straatsma, B. R., Allen, R. A., and Christensen, R. E.: The prophylaxis of retinal detachment. Trans. Pac. Coast Oto-ophthalmol. Soc. 46:211, 1965.

5. Chignell, A. H., and Shilling, J.: Propylaxis of retinal detachment. Br. J. Ophthalmol. 57:291, 1978.

6. Kanski, J. J., and Daniel, R.: Prophylaxis of retinal detachment. Am. J. Ophthalmol. 79:197, 1975.

7. Morse, P., and Scheie, H. G.: Prophylactic cryoretinopexy of retinal breaks. Arch. Ophthalmol. 92:204, 1974.

8. Tillery, W. V., and Lucier, A. C.: Round atrophic holes in lattice degeneration. An important cause of phakic retinal detachment. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:509, 1976.

9. Hyams, S. W., Neumann, E., and Friedman, Z.: Myopia - aphakia. II. Vitreous and peripheral retina. Br. J. Ophthalmol. 59:483, 1975.

10. Okun, E.: Gross and microscopic pathology in autopsy eyes. Part III. Retinal breaks without detachment. Am. J. Ophthalmol. 51:369, 1961.

11. Foos, R. Y.: Retinal holes. Am. J. Ophthalmol. 86:354, 1978.

12. Byer, N. E.: Clinical study of retinal breaks. Trans. Am. Acad. Ophthalmol. Otolaryngol. 71:461, 1967.

13. ———: Prognosis of asymptomatic retinal breaks. Arch. Ophthalmol. 92:208, 1974.

14. ———: The natural history of asymptomatic retinal breaks. Ophthalmology 89:1033, 1982.

15. ———: Long-term natural history of lattice degeneration of the retina. Ophthalmology 96:1396, 1989.

16. Michaelson, K., and Stein, R.: A study in the prevention of retinal detachment. Ann. Ophthalmol. 1:49, 1969.

17. Michaelson, K., Stein, R., Neuman, E., and Hyams, S.: A national cooperative study in the prevention of retinal detachment. In Pruett, R. C., and Regan, C. D. J. (eds.): Retina Congress. 25th Anniversary of the Retina Service Massachusetts Eye and Ear Infirmary. New York, Appleton-Century-Crofts, p. 661.

18. Hyams, S. W., Meir, E., Lury, M., Krakowski, D., Barkai, S., Jedwab, E., and Neumann, E.: Chorioretinal lesions predisposing to retinal detachment. 78:429, 1974.

19. Robertson, D. M., and Norton, E. W. D.: Long term follow-up of treated retinal breaks. Am. J. Ophthalmol. 75:395, 1973.

20. Combs, J. L., and Welch, R. B.: Retinal breaks without detachment. Natural history, management and long-term follow-up. Trans. Am. Ophthalmol. Soc. 80:64, 1982.

21. McPherson, A., O'Malley, R., and Beltangrady, S. S.: Management of the fellow eyes of patients with rhegmatogenous retinal detachment. Ophthalmology 88:922, 1981.

22. Folk, J. L., Arrindelle, L., and Klugman, M. R.: The fellow eye of patients with phakic lattice retinal detachment. Ophthalmology 96:72, 1989.

23. Benson, W. E., Grand, G., and Okun, E.: Aphakic retinal detachment. Management of the fellow eye. Arch. Ophthalmol. 93:245, 1975.

24. Crowley, J., and Hu, M.: Covariance analysis of heart transplant survival data. J. Am. Stat. Assoc. 72:27, 1977.

25. Goldberg, R. E., and Boyor, D. S.: Sequential retinal breaks following a spontaneous initial retinal break. Ophthalmology 88:10, 1980.

26. Davis, M. D.: Natural history of retinal breaks without detachment. Arch. Ophthalmol. 92:183, 1974.

27. Kraushar, M. F., and Morse, P. H.: The relationship between retinal surgery and preretinal macular fibrosis. Ophthalmic Surg. 19:843, 1988.

28. Benson, W. E.: Prophylactic therapy of retinal breaks. Surv. Ophthalmol. 22:41, 1977.

29. Jaffe, N. S., Clayman, H. M., and Jaffe, M. S.: Retinal detachment in myopic eyes after intracapsular and extracapsular cataract extraction. Am. J. Ophthalmol. 97:48, 1984.

30. Thomas, M.: Retinal detachments in high myopes. Management of the fellow eye. Ophthalmology 94(suppl.):98, 1987.

Neovascularization of the Iris in Rhegmatogenous Retinal Detachment

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To identify conditions associated with neovascularization of the iris in rhegmatogenous retinal detachment, we examined 36 eyes with this disorder seen at our hospital between 1979 and 1990. Clinical courses of disease were divided into the following three groups: (1) neovascularization of the iris without a history of a vitreoretinal operation (four eyes), (2) neovascularization of the iris after an unsuccessful vitreoretinal operation (26 eyes), and (3) neovascularization of the iris after surgical complications (six eyes). In all eyes of Groups 1 and 2, retinal detachment persisted at the onset of iris neovascularization; however, in six eyes, iris neovascularization subsided after retinal reattachment. Characteristic features of Groups 2 and 3 were patient age of 50 years or more, severe myopia, a history of increased intraocular pressure, a history of choroidal detachment, and a large scleral buckle.

NEOVASCULARIZATION of the iris in rhegmatogenous retinal detachment is encountered by most vitreoretinal surgeons, but little is known about this phenomenon. Blumenkranz and Hernandez[1] investigated it in rabbits and Stefansson and associates[2] investigated it in cats. They concluded that iris neovascularization occurred at a high rate when the retina was artificially detached in eyes on which pars plana vitrectomy and lensectomy had been performed. Uno and associates[3] reported clinical cases. They studied ten eyes that developed neovascularization of the iris within six months after an unsuccessful retinal detachment operation. We studied 36 eyes with neovascularization of the iris associated with rhegmatogenous retinal detachment seen at our hospital.

Patients and Methods

Our patients were included from the patients with 2,853 consecutive eyes with rhegmatogenous retinal detachment treated at our hospital between 1979 and 1990. Eyes with uveitis before the onset of retinal detachment, eyes with perforating injury or blunt trauma, and eyes with vascular disease of the retina or choroid were excluded because these factors could have influenced development of iris neovascularization.

Slit-lamp examination disclosed 36 of 2,853 eyes (1.3%) with abnormal vessels at the edge or surface of the iris, or at the anterior chamber angle during the course of treatment. The 36 eyes were divided into three groups according to the clinical course of disease before the onset of iris neovascularization. Group 1 consisted of four eyes that had no history of a vitreoretinal operation. One eye had no history of any ocular operations, but three were aphakic. Group 2 consisted of 26 eyes with a history of unsuccessful vitreoretinal operations. Of these 26 eyes, 11 had silicone oil in the vitreous, and 15 did not. The six eyes of Group 3 had complications from vitreoretinal operations. Three had mild anterior segment necrosis, whereas the other three had a history of vortex vein damage.

The following factors were analyzed in these 36 eyes: (1) incidence of persistent retinal detachment, (2) age, (3) refraction, (4) history of increased intraocular pressure (≥ 25 mm Hg for more than one week), (5) history of choroidal detachment, and (6) size and extent of the scleral buckle.

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Results

In all eyes of Groups 1 and 2, retinal detachment existed at the onset of iris neovascularization, whereas in two eyes of Group 3 it did not. Retinal detachment was not observed in one eye of Group 3 because of cataract. Iris neovascularization subsided after surgical reattachment of the retina in two eyes of Group 1 and in four eyes of Group 2.

In Group 2, consisting of eyes with persistent retinal detachment after an operation, 20 of 26 eyes (77%) were from patients who were 50 years or more of age. We measured refraction in nine eyes and four of these eyes (44%) were severely myopic (< -8 diopters). There was a history of increased intraocular pressure in four of 26 eyes (15%), a history of choroidal detachment in 12 of 21 eyes (57%), a wide scleral buckle of 9 mm or more in 12 of 22 eyes (55%), and a long scleral buckle extending 300 degrees or more in 20 of 24 eyes (83%).

In Group 3, consisting of eyes with complications from vitreoretinal operations, four of six eyes (67%) were from patients who were 50 years or more of age. We measured refraction in five eyes and two of these eyes (40%) were severely myopic (< -8 diopters). There was a history of increased intraocular pressure in four of six eyes (67%), a history of choroidal detachment in three of six eyes (50%), a wide scleral buckle of 9 mm or more in four of six eyes (67%), and a long scleral buckle extending 300 degrees or more in four of six eyes (67%).

Discussion

Retinal detachment persisted at the onset of iris neovascularization in all eyes of Groups 1 and 2. This was compatible with the experimental animal models of Blumenkranz and Hernandez[1] and Stefansson and associates,[2] which concluded that eyes without retinal detachment do not develop iris neovascularization. Group 3 was distinguished from the other two groups in that two eyes did not have retinal detachment at the onset of iris neovascularization. Interestingly, iris neovascularization subsided after surgical reattachment of the retina in six eyes of Groups 1 and 2. These clinical facts suggested that persistent retinal detachment had an essential role in the development of iris neovascularization. Bonnet[4] reported nine eyes with retinal neovascularization complicating long-term rhegmatogenous retinal detachment caused by trophic holes in the lattice degeneration or by ocular blunt trauma. In eight of these eyes, the retinal new vessel regressed after retinal reattachment. Conversely, Cunha-Vaz, Fonseca, and Vieira[5] demonstrated by two-point slit-lamp fluorophotometry that retinal blood flow was decreased in retinal detachment in humans. These reports, along with our study, suggest that decreased retinal circulation provokes neovascularization in eyes with retinal detachment. After retinal reattachment, improved retinal circulation may help the regression of the neovascularization.

Patient age of 50 years or more, severe myopia, a history of increased intraocular pressure, a history of choroidal detachment, a wide scleral buckle $\geq$ 9 mm, and a long scleral buckle $\geq$ 300 degrees were common features of the eyes in our Groups 2 and 3. Using fluorescein angiography, Yoshihara[6] reported that choroidal circulation was reduced in severely myopic eyes; using the ocular pulse amplitude as an index, Yoshida and associates[7] had the same result in eyes that had undergone scleral buckling procedures. Alm and Bill[8] reported that an artificial increase in ocular pressure reduced the rate of uveal blood flow in their experimental animal model of cats. On the basis of these reports, we considered the choroidal circulation in the eyes of our Groups 2 and 3 to be decreased. Three eyes of Group 3 had a history of vortex vein damage, and the other three eyes had a history of mild anterior segment necrosis. In the experimental animal model of Takahashi,[9] choroidal circulation was reduced in eyes with severed vortex veins, and in the animal model of Hayreh and Baines,[10] a filling defect of fluorescein in the choroid in eyes with occluded posterior ciliary arteries was found. These reports were the basis for our suggestion of a marked decrease of choroidal circulation in our Group 3 eyes with vortex vein damage and anterior segment necrosis in which the ciliary circulation might have been disturbed.

Brown and associates[11] reported 13 eyes with neovascular glaucoma in association with arterial obstructive disease and speculated that choroidal ischemia, in addition to retinal ischemia, might increase the chances of inducing ocular neovascularization, including neovascularization of the iris. That study suggested that, on the basis of persistent retinal detachment, reduced choroidal circulation may contribute to the development of iris neovascularization in rhegmatogenous retinal detachment. Although persistent retinal detachment may have an essential role in the development of iris neovascularization, the reduced choroidal circulation could have a more important role in some cases. In experimental animal models, Nakamura and associates proposed that iris neovascularization developed in eyes in which the long posterior ciliary arteries were occluded (Nakamura, R., Nakano, E., Wakabayashi, Y., Iwasaki, T., Agawa, T., and Usui, M., 94th Japanese Ophthalmological Society Meeting, May 24, 1990). In the two eyes with anterior segment necrosis in our Group 3, neovascularization of the iris developed without persistent retinal detachment at onset. The mechanism of iris neovascularization in these two eyes may be similar to that in the animal models of Nakamura and associates.

We speculated that two factors have an important role in the mechanism of iris neovascularization in rhegmatogenous retinal detachment. Persistent retinal detachment is an essential factor and reduced retinal circulation may lead to iris neovascularization. A second contributory factor may be the reduction of choroidal circulation caused by severe myopia, increased intraocular pressure, large scleral buckle, or surgical complications. Neovascularization of the iris is an ominous prognostic sign of rhegmatogenous retinal detachment. To prevent this condition, prompt reattachment of the retina and efforts to prevent the reduction of choroidal circulation are needed.

References

1. Blumenkranz, M. S., and Hernandez, E.: Rubeosis iridis and vitrectomy. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. St. Louis, C. V. Mosby, 1982, p. 234.

2. Stefansson, E., Landers, M. B. III, Wolbarsht, M. L., and Klintworth, G. K.: Neovascularization of the iris. An experimental model in cats. Invest. Ophthalmol. Vis. Sci. 25:361, 1984.

3. Uno, T., Sato, M., Danjo, S., Emi, K., Ikeda, T., and Tano, Y.: Rubeosis iridis following retinal detachment surgery. Jpn. Rev. Clin. Ophthalmol. 84:196, 1990.

4. Bonnet, M.: Peripheral neovascularization complicating rhegmatogenous retinal detachments of long duration. Graefes Arch. Clin. Exp. Ophthalmol. 225:59, 1987.

5. Cunha-Vaz, J. G., Fonseca, J. R., and Vieira, R.: Retinal blood flow in retinal detachment. Mod. Probl. Ophthalmol. 20:89, 1979.

6. Yoshihara, M.: Clinical studies on fundus changes and hemodynamics in degenerative myopes. Acta Soc. Ophthalmol. Jpn. 82:610, 1978.

7. Yoshida, A., Hirokawa, H., Fukui, Y., and Sakamoto, J.: Choroidal circulatory changes after scleral buckling procedures. Acta Soc. Ophthalmol. Jpn. 92:610, 1988.

8. Alm, A., and Bill, A.: Blood flow and oxygen extraction in the cat uvea at normal and high intraocular pressures. Acta Physiol. Scand. 80:19, 1970.

9. Takahashi, S.: Studies on choroidal blood flow using the hydrogen clearance method. III. Effects of vortex vein occlusion. Folia Ophthalmol. Jpn. 33:958, 1982.

10. Hayreh, S. S., and Baines, J. A. B.: Occlusion of the posterior ciliary artery. I. Effects on choroidal circulation. Br. J. Ophthalmol. 56:719, 1972.

11. Brown, G. C., Magargal, L. E., Simeone, F. A., Goldberg, R. E., Federman, J. L., and Benson, W. E.: Arterial obstruction and ocular neovascularization. Ophthalmology 89:139, 1982.

Bone Marrow Transplant Retinopathy

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Five of eight patients (62%) who survived at least six months after autologous or allogeneic bone marrow transplantation for acute leukemia developed occlusive microvascular retinopathy. Treatable retinal microangiopathy included a high incidence (80%) of clinically significant macular edema and one case of proliferative retinopathy with subhyaloid hemorrhage. The bone marrow transplant protocol required high-dose cytarabine hydrochloride and 1,200 cGy of total body irradiation. The development of radiation retinopathy after such low doses of teletherapy suggests that high-dose chemotherapy may increase the susceptibility for the development of retinopathy at otherwise safe radiation doses.

BONE MARROW TRANSPLANTATION has assumed an increasingly important role in the treatment of both primary and relapsed acute leukemia.[1] In this treatment, radiotherapy and high-dose chemotherapy are combined to eradicate leukemic cells from the body and bone marrow. A principal side effect of this treatment is destruction of healthy bone marrow (bone marrow ablation), which may result in high patient morbidity and mortality unless the damaged bone marrow can be replaced. This is accomplished in two ways. After initial remission induction with chemotherapy, autologous bone marrow may be harvested from leukemic patients for later transplantation. Alternatively, allogeneic bone marrow may be harvested from a healthy HLA-compatible donor. When available, allogeneic bone marrow is uncontaminated by residual leukemic cells. Allogeneic bone marrow transplants are, however, predisposed to developing graft-vs-host disease.

Ocular complications of bone marrow transplantation may be divided into those involving either the anterior or posterior segment. Ocular anterior segment complications of bone marrow transplantation have been well-described.[2-8] Ocular posterior segment complications, however, are less well known.[9]

Recently, a high incidence of occlusive microvascular retinopathy has been discovered among the long-term survivors of both autologous and allogeneic bone marrow transplantation for acute leukemia in which a standard protocol of total body irradiation and high-dose cytarabine hydrochloride had been used.[10] We studied the detailed characteristics of bone marrow transplant retinopathy.

Patients and Methods

Between 1983 and 1990, 30 patients with either acute lymphocytic leukemia in remission, or acute myelocytic leukemia in second or subsequent remission or early relapse underwent autologous or allogeneic bone marrow transplantation at Emory University Hospital. The standard protocol for bone marrow ablation included high-dose cytarabine hydrochloride and total body irradiation.[10] Treatment of all patients consisted of the intravenous administration of 3 g of cytarabine hydrochloride per square meter over a 75- to 90-minute time period every 12 hours for 12 doses followed by 1,200 cGy of total body irradiation in 200-cGy fractions, every 12 hours for a three-day period. Additionally, patients with acute lymphocytic

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leukemia had received 1,800 to 2,400 cGy of prophylactic cranial irradiation during their initial remission induction therapy, one to 47 months (median, three months) before total body irradiation. One patient (Patient 4), who had central nervous system leukemia, received an additional 1,080 cGy of craniospinal irradiation two months before bone marrow ablation.

Allogeneic bone marrow transplant recipients received the following prophylaxis against graft-vs-host disease: cyclosporine, 1.5 mg/kg of body weight intravenously every 12 hours beginning the day before bone marrow transplantation; and five doses of methotrexate, 15 mg/m^2 intravenously on Day 1, and 10 mg/m^2 on Days 1, 3, 6, and 11 after bone marrow transplantation.[11] None of the patients described developed graft-vs-host disease with this protocol. The supportive care provided to the patients, which is detailed elsewhere, included prompt correction of anemia and thrombocytopenia with irradiated blood products.[10]

We studied the findings in the eight patients who survived at least six months after bone marrow transplantation using this protocol. All patients underwent complete ophthalmic examinations including fundus biomicroscopy, stereoscopic color fundus photography, and fluorescein angiography. No patient had any preexisting ocular or systemic disorder associated with retinal vascular disease.

Results

The characteristics of the eight patients with bone marrow transplants who survived at least six months were analyzed (Table 1). Five of the eight patients (62%) had developed bone marrow transplant retinopathy after a median of 11 months after bone marrow ablation (range, seven to 25 months). Bone marrow transplant retinopathy appeared predominantly in young white males who survived this procedure.

Of the five patients who developed bone marrow transplant retinopathy, three (60%) had acute lymphocytic leukemia and two (40%) had acute myelocytic leukemia. In the three survivors who did not develop bone marrow transplant retinopathy, two (66%) had acute myelocytic leukemia and one (33%) had acute lymphocytic leukemia. Of the five patients who manifested bone marrow transplant retinopathy, three (60%) had allogeneic transplants and two (40%) had autologous transplants as compared with two (66%) allogeneic transplants and one (33%) autologous transplant in the group that did not manifest bone marrow transplant retinopathy.

The average total radiation dose absorbed by the posterior retina of those patients who developed bone marrow transplant retinopathy was 2,736 cGy as compared with the 1,200-cGy average dose in the patients who did not develop bone marrow transplant retinopathy. Patients with bone marrow transplant retinopathy may be further subdivided into two groups on the basis of leukemic diagnosis and radiation dose. Three of the five patients (60%) with bone marrow transplant retinopathy had acute lymphocytic leukemia and received prophylactic cranial irradiation, one to 47 months before total body irradiation and chemotherapy with cytarabine hydrochloride. One patient (Patient 4) in this subgroup received an additional craniospinal irradiation dose for central nervous system leukemia, two months before transplantation. The average radiation dose absorbed by the posterior retina of the subgroup of patients with bone marrow transplant retinopathy who had acute lymphocytic leukemia was 3,560 cGy. In contrast, two of the five patients with bone marrow transplant retinopathy (40%) had acute myelocytic leukemia and did not receive supplemental cranial or craniospinal radiation. These patients developed bone marrow transplant retinopathy after receiving just 1,200 cGy of total body irradiation. The type and incidence of bone marrow transplant retinopathy in the 16 eyes of the eight survivors were determined according to bone marrow transplant type and radiation dose (Table 2). All six patients (100%) who received total body irradiation plus prophylactic cranial irradiation developed bone marrow transplant retinopathy. In comparison, four of the ten (40%) patients who received total body irradiation alone developed bone marrow transplant retinopathy.

Not only did the incidence of bone marrow transplant retinopathy increase with increasing total radiation dose, but so did the severity of the retinopathy. Generally, the higher the total radiation dose absorbed by the posterior retina, the greater was the severity of the retinopathy. Patient 5, who developed proliferative retinopathy in both eyes, was the one exception. Although he possessed the most severe category of retinopathy (proliferative), he had received only the second highest total dose of radiation (Table 1). However, he had received his prophylactic irradiation only one month before bone

TABLE 1

SUMMARY OF EIGHT PATIENTS WHO UNDERWENT BONE MARROW TRANSPLANTATION

PATIENT NO., AGE (YRS), RACE, GENDER	DIAGNOSIS	BONE MARROW TRANSPLANTATION TYPE	RADIATION DOSE (C GY)	INTERVAL TO RETINOPATHY (MOS)	VISUAL ACUITY	TYPE OF RETINOPATHY
1, 25, white, M	Acute myelocytic leukemia	Autologous	Total body irradiation, 1,200 Cranial irradiation, 0 Total, 1,200	25	R.E.: 20/40 L.E.: 20/60	Nonproliferative retinopathy and macular edema Nonproliferative retinopathy and macular edema
2, 29, white, M	Acute myelocytic leukemia	Allogeneic	Total body irradiation, 1,200 Cranial irradiation, 0 Total, 1,200	11	R.E.: 20/200 L.E.: 20/200	Nonproliferative retinopathy and macular edema Nonproliferative retinopathy
3, 29, black, F	Acute lymphocytic leukemia	Allogeneic	Total body irradiation, 1,200 Cranial irradiation, 2,400 Total, 3,600	18	R.E.: 20/80 L.E.: 20/80	Nonproliferative retinopathy and macular edema Nonproliferative retinopathy and macular edema
4, 27, white, M	Acute lymphocytic leukemia	Autologous	Total body irradiation, 1,200 Cranial irradiation, 2,400 Craniospinal irradiation, 1,080 Total, 4,680	7	R.E.: 20/20 L.E.: 20/20	Nonproliferative retinopathy Nonproliferative retinopathy
5, 17, white, M	Acute lymphocytic leukemia	Allogeneic	Total body irradiation, 1,200 Cranial irradiation, 1,800 Total, 3,000	11	R.E.: 20/60 L.E.: 20/25	Proliferative and nonproliferative retinopathy with macular edema Proliferative and nonproliferative retinopathy with macular edema
6, 52, white, F	Acute myelocytic leukemia	Autologous	Total body irradiation, 1,200 Total, 1,200	15*	R.E.: 20/15 L.E.: 20/20	None None
7, 31, black, F	Acute myelocytic leukemia	Allogeneic	Total body irradiation, 1,200 Total, 1,200	7*	R.E.: 20/20 L.E.: 20/25	None None
8, 32, black, F	Acute lymphocytic leukemia	Allogeneic	Total body irradiation, 1,200 Total, 1,200	16*	R.E.: 20/40 L.E.: 20/40	None None

*No retinopathy developed during this follow-up interval.

marrow ablation (total body irradiation and high-dose cytarabine hydrochloride). In comparison, Patient 4, given the highest total radiation dose, did not undergo bone marrow ablation until 47 months after receiving prophylactic cranial irradiation. This finding may suggest that the interval between prophylactic irradiation and bone marrow ablation (total body irradiation and high-dose cytarabine hydrochloride) may be an important variable in determining the incidence or severity of bone marrow transplant retinopathy, or both (the shorter the interval, the greater the severity of retinopathy).

A less dramatic correlation existed between bone marrow transplant retinopathy and the type of leukemia. Bone marrow transplant retinopathy developed in 75% of the survivors with acute lymphocytic leukemia as compared with a 50% incidence in those surviving acute myelocytic leukemia. However, as previously discussed, leukemia type and radiation doses were covariate. In general, the patients with acute lymphocytic leukemia received prophy-

TABLE 2
TYPE AND INCIDENCE OF BONE MARROW TRANSPLANT RETINOPATHY

CLINICAL CHARACTERISTIC	NO. OF EYES WITH NO DISEASE (%)	EYES WITH NONPROLIFERATIVE RETINOPATHY: WITHOUT MACULAR EDEMA (%)	EYES WITH NONPROLIFERATIVE RETINOPATHY: WITH MACULAR EDEMA (%)	EYES WITH PROLIFERATIVE RETINOPATHY* (%)
Acute lymphocytic leukemia (8 eyes)	2/8 (25)	2/8 (25)	4/8 (50)	2/8 (25)
Acute myelocytic leukemia (8 eyes)	4/8 (50)	1/8 (12)	3/8 (37)	0/8 (0)
Allogeneic bone marrow transplant (10 eyes)	4/10 (40)	1/10 (10)	5/10 (50)	2/10 (20)
Autologous bone marrow transplant (6 eyes)	4/6 (67)	2/6 (33)	2/6 (33)	0/6 (0)
Total body irradiation (10 eyes)	6/10 (60)	1/10 (10)	3/10 (30)	0/10 (0)
Total body irradiation and cranial irradiation (6 eyes)	0/6 (0)	2/6 (33)	4/6 (67)	2/6 (33)

*Macular edema was apparent in both eyes of this patient.

lactic cranial irradiation in addition to total body irradiation, whereas the patients with acute myelocytic leukemia received total body irradiation alone. Indeed, the only patient with acute lymphocytic leukemia (Patient 8) who received total body irradiation alone did not develop bone marrow transplant retinopathy. These findings suggested that cumulative total radiation dose is a critical independent variable in the development of bone marrow transplant retinopathy.

Likewise, no significant correlation between the incidence of bone marrow transplant retinopathy and bone marrow transplant type was evident, when corrected for differences in radiation dose between the two groups. Patients with both allogeneic and autologous bone marrow transplants had similar incidences of bone marrow transplant retinopathy (40% vs 33%, respectively).

The median visual acuity in the five patients who developed bone marrow transplant retinopathy was 20/50 as compared to a median visual acuity of 20/20 in the three patients without retinopathy. The visual acuity in eyes with bone marrow transplant retinopathy ranged from 20/20 in those without macular edema to 20/200 in eyes with severe macular edema.

The retinal findings in the ten eyes of the five patients with bone marrow transplant retinopathy were analyzed (Table 3). Generally, retinal findings tended to be bilaterally symmetric. Retinal telangiectases and capillary remodeling developed universally at the edge of the foveal avascular zone, especially temporally, where minor amounts of capillary dropout were uniformly detected (Figs. 1 through 3). Telangiectases were also intermittently scattered elsewhere in the posterior pole and midperiphery. Microaneurysms, in contrast, were predominantly sparsely scattered in the posterior pole and midperiphery, generally away from the edge of the foveal avascular zone.

Clinically significant macular edema, defined as biomicroscopically evident retinal thickening within ⅓ disk diameter (500 μm) of the center of the foveal avascular zone and associat-

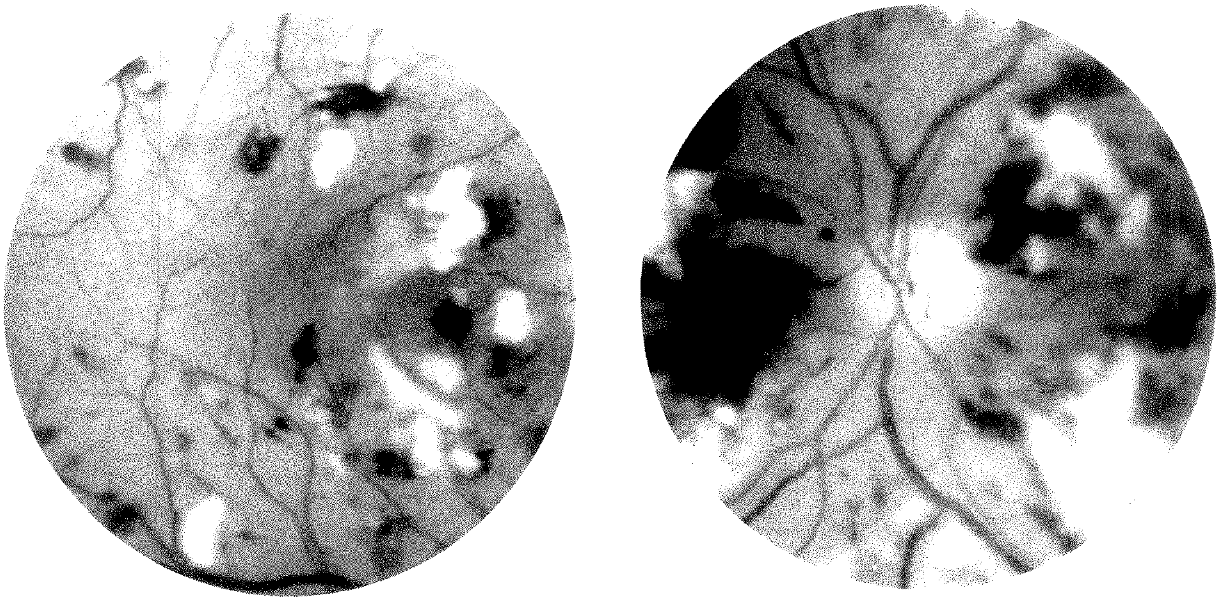

Fig. 2 (Lopez and associates). Patient 4. Right (left) and left (right) eyes showing multiple cotton-wool spots, flame and blot hemorrhages, macular edema, microaneurysms, and retinal capillary telangiectases.

loss of retinal capillary endothelial cells and pericytes. Cotton-wool spots were seen as the areas of retinal capillary loss became confluent. These faded later, resulting in areas of retinal capillary nonperfusion, which were only visible on fluorescein angiography. Histopathologic studies disclosed that the first identifiable changes involved the deep retinal capillary plexus. Larger retinal vessels were subsequently involved, sometimes manifesting myointimal proliferation and hyalinization.[16-18] Intraretinal neovascularization was seen; however, no reti-

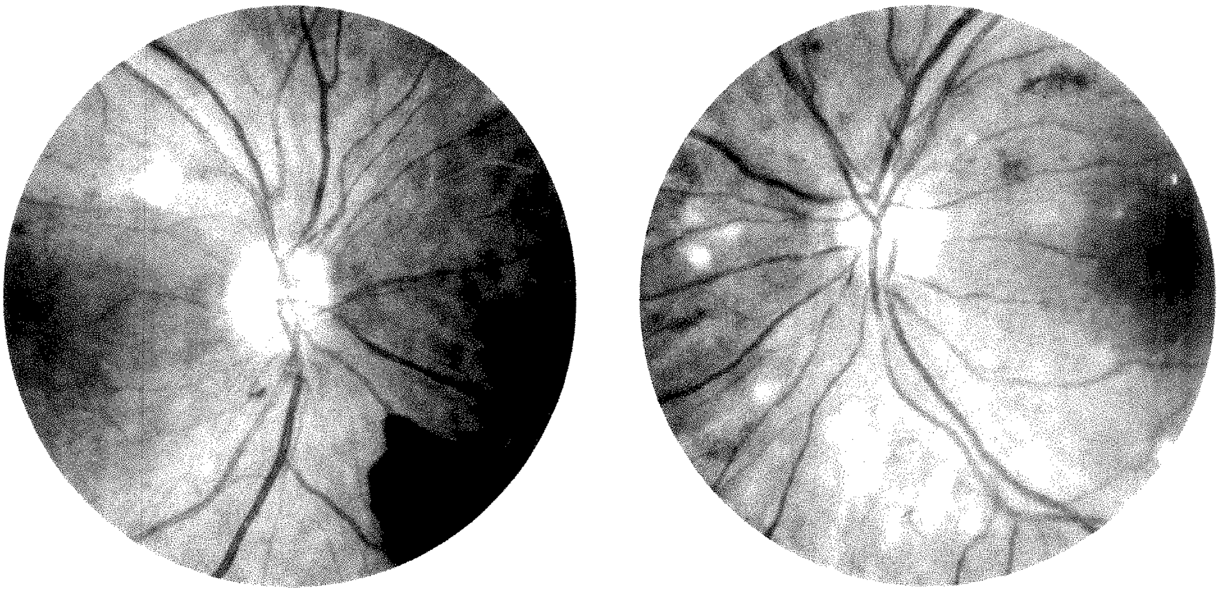

Fig. 3 (Lopez and associates). Patient 5. In the right eye (left), a subhyaloid hemorrhage along the inferonasal arcade covers an area of retinal neovascularization. Fine neovascularization is also present along the superior margin of the optic disk in the left eye (right). Bilateral macular edema, vascular sheathing, multiple cotton-wool spots, microaneurysms, retinal capillary telangiectases, and flame and blot hemorrhages were also found.

nal or disk neovascularization developed in this model. Iris neovascularization and neovascular glaucoma developed in these monkeys after 2½ to 3½ years.

The neural retina, like the central nervous system, is highly resistant to radiation damage, but the retinal microvasculature is not. Generally, administration of radiation results in preferential damage to the blood vessels of the inner retinal layers and spares the retinal photoreceptors, neural cells, and glia.[19] Animal studies have shown that cone photoreceptors are particularly radioresistant, requiring single doses of radiation in excess of 10,000 cGy before marked histopathologic changes are evident.[19] Radiation damage to the choroidal vasculature with resultant choroidal infarction develops much less frequently.[20]

Radiation retinopathy has been reported after irradiation of intraocular tumors, orbital tumors, sinus tumors, and pituitary tumors.[21-25] This retinopathy can be seen after irradiation administered by brachytherapy, using orbital seeds or episcleral plaques; or teletherapy, using external beam radiation, helium ions, or protons. Typically, the microangiopathy becomes apparent six or more months after treatment, although some cases are not seen until three years after treatment. In a report by Brown and associates,[24] the time of onset of radiation retinopathy with external beam radiation ranged from seven to 36 months, with a mean of 18.7 months. This was similar in range, but slightly later on average (18.7 months vs 14.4 months) than the time of onset in our patients with bone marrow transplant retinopathy. However, differences in the length of follow-up are important because the prevalence of radiation retinopathy increases with longer follow-up.

The radiation dose with which retinopathy is seen varies from report to report. It is uncommon for radiation retinopathy to be reported after conventionally fractionated irradiation with less than 3,000 cGy.[26] In two reports, 50% of patients developed radiation retinopathy after 6,000 cGy, whereas 85% to 95% of patients had changes after 7,000 to 8,000 cGy.[27,28] A 5% incidence of this complication was reported to develop after irradiation with 4,500 cGy administered to the retina, in 180- to 200-cGy fractions. In the series reported by Brown and associates,[24] the mean dose required to induce foveal damage using teletherapy with external beam radiation was 4,900 cGy, with a range of 3,500 to 7,200 cGy. The maximal absorbed dose to the posterior retina was 3,600 cGy for the two patients who received prophylactic cranial irradiation and 4,680 cGy for the patient (Patient 4) who received additional cranial irradiation and craniospinal irradiation for his central nervous system leukemia. The maximal absorbed dose to the posterior retina in patients receiving total body irradiation alone was 1,200 cGy. The likelihood that three to six patients would develop marked retinopathy from less than 3,700 cGy is small. Two patients who received only 1,200 cGy developed retinopathy, which suggested that other factors were operative. Because radiation is considered to induce retinopathy through damage to the retinal vascular endothelium and pericytes, it is possible that other aspects of the protocol may have been contributory. In no case was anemia, thrombocytopenia, or graft-vs-host disease indicated as contributing to the retinopathy.

The incidence of radiation-induced tissue damage increases with radiation dose rate or fraction size.[24] For ocular and orbital tumors, the usual dosage is 200 to 300 cGy/day, given over a one- to two-month period for a total dose of 3,500 to 7,200 cGy.[24] Total body irradiation was administered to the patients with bone marrow transplants at a higher daily dose (400 cGy/day), but divided into two fractions and in a much smaller total dose (1,200 cGy). Even with this altered fractionation scheme, this case of radiation retinopathy was induced by exceptionally low radiation doses.[29,30] In a long-term follow-up study of over 1,000 patients with bone marrow transplants, which used a similar radiation protocol, but a somewhat different chemotherapeutic regimen, radiation retinopathy was not evident in any patient.[31]

Prophylaxis of graft-vs-host disease with cyclosporine has been associated with the development of an occlusive microvascular retinopathy characterized by multiple cotton-wool spots and retinal hemorrhages in one report of three recipients of allogeneic bone marrow transplants with acute leukemia.[9] All three patients underwent a bone marrow ablation protocol that included high-dose cyclophosphamide and 1,000 cGy of total body irradiation. All of the patients had received 2,000 to 2,400 cGy of additional prophylactic cranial irradiation during initial remission induction therapy, three to ten months before bone marrow transplantation. The onset of the retinopathy was observed nine to 16 months after total body irradiation and chemotherapy and was primarily attributed to the effects of the cyclosporine, although the supplemental cranial irradiation was considered contributory.

TABLE 3
RETINAL FINDINGS IN EYES WITH BONE MARROW TRANSPLANT RETINOPATHY

FINDING	EYES WITH ALLOGENEIC BONE MARROW TRANSPLANT (N = 6)	EYES WITH AUTOLOGOUS BONE MARROW TRANSPLANT (N = 4)	EYES WITH TOTAL BODY IRRADIATION (N = 4)	EYES TREATED WITH TOTAL BODY IRRADIATION AND CRANIAL IRRADIATION (N = 6)
Telangiectasia	6 (100%)	4 (100%)	4 (100%)	6 (100%)
Microaneurysm	6 (100%)	4 (100%)	4 (100%)	6 (100%)
Cotton-wool spots	6 (100%)	2 (50%)	3 (75%)	6 (100%)
Macular edema	6 (100%)	2 (50%)	3 (75%)	4 (67%)
Blot hemorrhage	6 (100%)	2 (50%)	4 (100%)	4 (67%)
Flame hemorrhage	4 (67%)	1 (25%)	2 (50%)	2 (33%)
Hard exudate	1 (17%)	2 (50%)	0 (0%)	3 (50%)
Sheathed vessels	2 (33%)	0 (0%)	0 (0%)	2 (33%)
Neovascularization	2 (33%)	0 (0%)	0 (0%)	2 (33%)
Vitreous hemorrhage	1 (17%)	0 (0%)	0 (0%)	1 (17%)

ed with retinal vascular leakage on fluorescein angiography, was observed in eight of ten (80%) eyes with bone marrow transplant retinopathy (Figs. 1 through 3). Macular edema in these patients with retinopathy was primarily diffuse rather than circinate. Stereoscopic fluorescein angiography disclosed leakage from perifoveal retinal telangiectases, especially those in the deep retinal capillary plexus, as the predominant source of the macular edema (Fig. 1). Perifoveal microaneurysms were an infrequent source of macular edema, a finding which may explain the diffuse nature of the macular edema, as well as the scarcity of circinate rings and hard exudates in these patients. In all cases, clinically significant macular edema appeared to explain decrease in visual acuity.

Vascular attenuation and sheathing of second- and third-order retinal arterioles (Fig. 3) were observed in both eyes of the most severely affected patient (Patient 5). This patient had allogeneic bone marrow transplantation for acute lymphocytic leukemia after prophylactic cranial irradiation one month earlier. His right eye developed retinal neovascularization along the inferonasal arcade associated with subhyaloid hemorrhage (Fig. 3, left), and his left eye developed disk neovascularization (Fig. 3, right). Panretinal photocoagulation was performed with subsequent involution of the retinal neovascularization. Macular edema was observed in both eyes and accounted for the reduced visual acuity of R.E.: 20/60 and L.E.: 20/25.

Two years after bone marrow transplantation, progressive posterior subcapsular cataracts reduced his visual acuity to 20/200 in both eyes. Successful extracapsular cataract extraction and intraocular lens implantation was performed in the left eye. Postoperatively, however, visual acuity remained at 20/200 in his left eye, secondary to an exacerbation of his macular edema. Treatment with periocular injections of corticosteroids was subsequently performed in this eye, and visual acuity improved to 20/60.

Discussion

The constellation of clinical findings in these patients with bone marrow transplants is most consistent with what has been called radiation retinopathy. This condition was described by Stallard in 1933.[12] The clinical signs include the following: cotton-wool spots, retinal hemorrhages, microaneurysms, lipid exudates, capillary nonperfusion, cystoid macular edema, retinal neovascularization, vitreous hemorrhage, traction retinal detachment, optic atrophy, rubeosis iridis, and neovascular glaucoma.[12-14] These changes are believed to reflect radiation damage to the retinal vascular endothelium and pericytes.[15-17]

Gragoudas and associates[15] chronicled the evolution of radiation retinopathy in monkeys treated with a single 3,000-cGy dose of teletherapy. The first changes seen involved focal

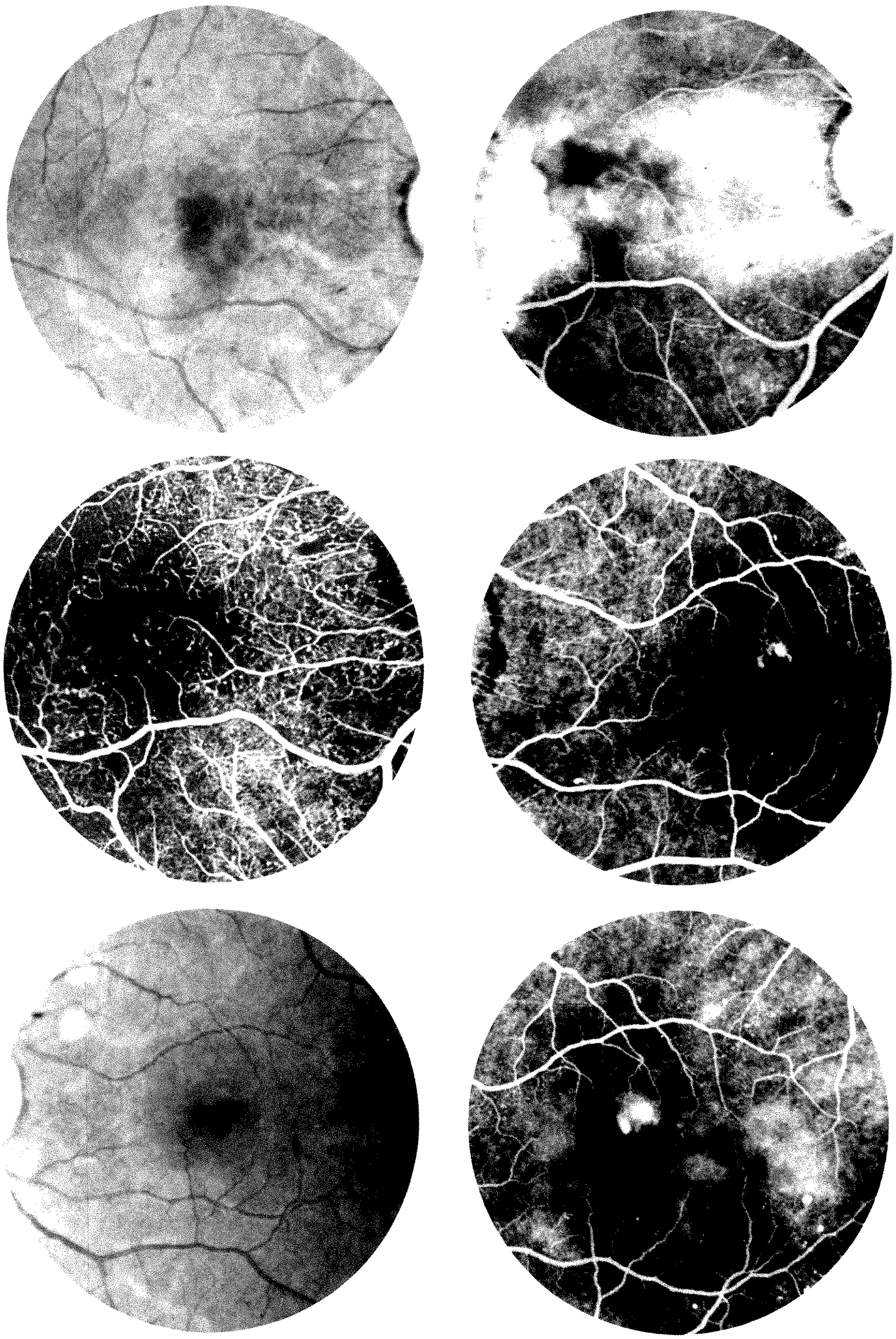

Fig. 1 (Lopez and associates). Patient 3. Red-free photographs with corresponding early and late arteriovenous phases of the fluorescein angiogram of the right (left; top, middle, bottom) and left eye (right; top, middle, bottom), respectively. Bilateral macular edema, cotton-wool spots, blot hemorrhages, microaneurysms, and retinal capillary telangiectases were found.

Neither the cyclosporine nor the methotrexate used in the prophylaxis of graft-vs-host disease in our recipients of allogeneic bone marrow transplants appeared to contribute considerably to the development of the accelerated radiation retinopathy seen in our patients. First, the incidence or severity of bone marrow transplant retinopathy was not markedly different, when corrected for differences in total radiation dose, in the patients with autologous bone marrow transplants (who were not treated with cyclosporine or methotrexate) as compared with the patients with the allogeneic bone marrow transplants who were treated with both of these agents as prophylaxis against graft-vs-host disease. Second, 40% of patients with bone marrow transplant retinopathy had undergone autologous transplantation using a regimen that did not include either of these two agents.[10]

The retinal findings, time of onset of the retinopathy, and the radiation protocol used in the three patients described by Gloor and associates[9] were similar to those factors in our patients with bone marrow transplant retinopathy. It is possible, without the benefit of a control group who developed retinopathy but were not treated with cyclosporine, that the contribution of cyclosporine to the development of retinopathy may have been overestimated, relative to the radiation effects. The cases described by Gloor and associates[9] support our conclusion that the likelihood of patients with leukemia who have received previous prophylactic cranial irradiation to develop radiation retinopathy after bone marrow transplantation is increased. Additionally, their findings suggested that an accelerated radiation retinopathy may develop using high-dose chemotherapeutic agents other than cytarabine hydrochloride (that is, cyclophosphamide).[9]

Beside total body irradiation, the only feature of the bone marrow transplant protocol common to all the patients who developed bone marrow transplant retinopathy was the use of high-dose cytarabine hydrochloride. The high doses of cytarabine hydrochloride required in this protocol appear to be the major source of the accelerated radiation retinopathy in these patients. The pathogenesis of this effect entails radiosensitization of the retinal vasculature by the high-dose chemotherapy. Similar radiosensitization by high-dose cytarabine hydrochloride has been previously described in both bacteria and mammalian cells.[32-34]

Radiation retinopathy reflects radiation damage to the DNA of the retinal vascular endothelium and pericytes by a number of different mechanisms.[34,35] Radiation, for example, causes the radiolysis of water into highly reactive oxygen species, such as hydroxyl ions and free radicals, that may chemically interact with the sugar phosphate backbone of DNA resulting in DNA strand scission.[35-39] Fragmentation of DNA prevents replication and may culminate in cell death. Insight into the mechanism of radiation-induced damage and radiosensitization may be gleaned from an examination of the radiation dose-response curve (Fig. 4).[39,40]

The radiation dose-response curve relates the logarithm of radiation toxicity or cell death, on the ordinate axis, to the radiation dose on the abscissa (Fig. 4).[39,40] The initial portion of this curve, known as the shoulder, is composed of a relatively flat segment followed by a downward curve, which marks the transition to a steep dose-response portion. The initial relatively flat portion of the shoulder represents repair by the cell of sublethal radiation-induced DNA damage.[37,39,40] For example, this may involve enzymatic repair of DNA strand scission by the enzyme DNA polymerase.[34] The downward curve of the shoulder reflects the radiation dose at which the cellular repair mechanisms can no longer compensate for damage to the DNA.[37,39,40] Any further increase in radiation dose results in exponential cell death that is independent of the DNA repair mechanisms that have now been overwhelmed. This is represented by the steeper downward sloping portion of the curve.

Radiosensitization develops when the lethal effects of a chemotherapeutic agent are additive or supra-additive to those of the radiation.[37,40] Graphically, this may be represented by a shift of the radiation dose-response curve to the left (Fig. 4). The resultant shortening of the width of the shoulder of the curve indicates a lowering of the threshold safe dose of radiation that will not result in radiation retinopathy. Conversely, radiation retinopathy may now develop at radiation doses previously considered safe. Just such an effect is clinically evident in our patients with bone marrow transplants who developed radiation retinopathy after a dose of only 1,200 cGy of total body irradiation.

The method by which high-dose cytarabine hydrochloride shifts the radiation dose-response curve to the left and shortens the width of the shoulder of the curve is related to its mechanism of action. Cytarabine hydrochloride is a pyrimidine antagonist antimetabolite that functions by inhibiting DNA polymerase, a crucial enzyme in DNA replication and repair processes.[41,42] No doubt DNA polymerase has a

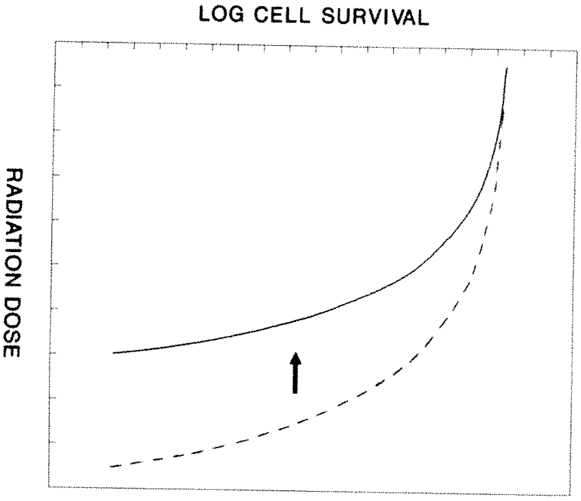

Fig. 4 (Lopez and associates). The radiation dose-response curve relates the logarithm of the number of surviving cells on the ordinate axis to the radiation dose in cGy on the abscissa (dotted line). Radiosensitization by high-dose cytarabine hydrochloride shifts the radiation dose-response curve to the left (solid line), resulting in a reduction in the width of the shoulder of the curve.

pivotal role in the repair of radiation-induced DNA damage within the retinal vascular endothelium and pericytes, such as in the repair of DNA strand scission.[33,38] Inhibition of this enzyme by high-dose cytarabine hydrochloride protocol curtails the DNA repair processes that are responsible for the width of the shoulder of the radiation-dose response curve, resulting in a shift of the curve to the left.

In addition to lowering the threshold dose for radiation retinopathy, the shift of the curve to the left indicates that the severity of the radiation damage or radiation retinopathy will be greater at any given radiation dose with chemotherapy than without it. This was perhaps most clinically evident in Patient 5, who developed proliferative retinopathy with macular edema after a total radiation dose of just 3,000 cGy (Table 1).

It should be stressed that the effects of radiation-induced DNA damage are cumulative and are accentuated by the high-dose chemotherapy that prevents DNA repair. This cumulative radiation effect was reflected in the increased incidence and severity of the radiation retinopathy in the patients with bone marrow transplants who had received additional prophylactic cranial irradiation one to several months before total body irradiation.

Clinically, bone marrow transplant retinopathy is characterized by a high incidence of potentially treatable retinal vascular lesions (eight of the ten eyes [80%] had clinically remarkable radiation-induced macular edema and one eye even had proliferative radiation retinopathy with vitreous hemorrhage [Patient 5]). The macular edema in this condition is primarily diffuse, resulting from perifoveal telangiectasis, and generally requires grid retinal photocoagulation for treatment. The natural course of the clinically significant macular edema in this condition is not well known and may include progressive microvascular occlusion with macular nonperfusion and irreversible visual loss in the long term. However, because these are young patients with often limited life spans, treatment of visually remarkable macular edema should be considered, especially when important daily activities such as driving are threatened.

Panretinal scatter photocoagulation has been advocated for eyes with proliferative radiation retinopathy and one or more high-risk factors (as defined by the Diabetic Retinopathy Study)[43] to prevent visually disabling vitreous hemorrhage and traction retinal detachment.[44] Although the natural course of proliferative retinopathy in this condition is poorly understood, the favorable response of the retinopathy to panretinal photocoagulation observed in both our patient and others with radiation retinopathy[44,45] suggested that this therapy merits careful consideration.

References

1. Santos, G. W., and Kaizer, H.: Bone marrow transplantation in acute leukemia. Semin. Hematol. 19:227, 1982.
2. Jack, M. K., and Hicks, J. D.: Ocular complications in high-dose chemoradiotherapy and marrow transplantation. Ann. Ophthalmol. 13:709, 1981.
3. Franklin, R. M., Kenyon, K. R., Tutschka, P. J., Saral, R., Green, W. R., and Santos, G. W.: Ocular manifestations of graft-versus-host disease. Ophthalmology 90:4, 1983.
4. Hirst, L. W., Jabs, D. A., Tutschka, P. J., Green, W. R., and Santos, G. W.: The eye in bone marrow transplantation. I. Clinical study. Arch. Ophthalmol. 101:580, 1983.
5. Jabs, D. A., Hirst, L. W., Green, W. R., Tutschka, P. J., Santos, G. W., and Beschorner, W. E.: The eye in bone marrow transplantation. II. Histopathology. Arch. Ophthalmol. 101:585, 1983.

6. Hanada, R., and Ueoka, Y.: Obstruction of nasolacrimal ducts closely related to graft-versus-host disease after bone marrow transplantation. Bone Marrow Transplant. 4:125, 1989.

7. Livesey, S. J., Holmes, J. A., and Whittaker, J. A.: Ocular complications of bone marrow transplantation. Eye 3:271, 1989.

8. Sanders, J. E.: Late effects in children receiving total body irradiation for bone marrow transplantation. Radiother. Oncol. 18(suppl.):82, 1990.

9. Gloor, B., Gratwohl, A., Hahn, H., Kretzschmar, S., Robert, Y., Speck, B., and Daicker, B.: Multiple cotton wool spots following bone marrow transplantation for treatment of acute lymphatic leukaemia. Br. J. Ophthalmol. 69:320, 1985.

10. Vogler, W. R., Winton, E. F., Heffner, L. T., Gordon, D. S., Sternberg, P., Crocker, I., Reynolds, R., and Dobbs, C. K.: Ophthalmological and other toxicities related to cytosine arabinoside and total body irradiation as preparative regimen for bone marrow transplantation. Bone Marrow Transplant. 6:405, 1990.

11. Storb, R., Deeg, H. J., Whitehead, J., Applebaum, F., Beatty, P., Bensinger, W., Buckner, C. D., Clift, R., Doney, K., Farewell, V., Hansen, J., Hill, R., Lum, L., Martin, P., McGuffin, R., Sanders, J., Stewart, P., Sullivan, K., Witherspoon, R., Yee, G., and Thomas, E. D.: Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft-versus-host disease after marrow transplantation for leukemia. N. Engl. J. Med. 314:729, 1986.

12. Stallard, H. B.: Radiant energy as (A) a pathogenic (B) a therapeutic agent in ophthalmic disorders. Br. J. Ophthalmol. 6(suppl.):1, 1933.

13. Gass, J. D. M.: A fluorescein angiographic study of macular dysfunction secondary to retinal vascular disease. VI. X-ray irradiation, carotid artery occlusion, collagen vascular disease, and vitritis. Arch. Ophthalmol. 80:606, 1968.

14. Hayreh, S. S.: Post-radiation retinopathy. A fluorescence fundus angiographic study. Br. J. Ophthalmol. 54:705, 1970.

15. Gragoudas, E. S., Zakov, N. Z., Albert, D. M., and Constable, I. J.: Long-term observations of proton-irradiated monkey eyes. Arch. Ophthalmol. 97:2184, 1979.

16. Irvine, A. R., Alvarado, J. A., Wara, W. M., Morris, B. W., and Wood, I. S.: Radiation retinopathy. An experimental model for the ischemic-proliferative retinopathies. Trans. Am. Ophthalmol. Soc. 79:103, 1981.

17. Irvine, A. R., and Wood, I. S.: Radiation retinopathy as an experimental model for ischemic proliferative retinopathy and rubeosis iridis. Am. J. Ophthalmol. 103:790, 1987.

18. Egbert, P. R., Fajardo, L. F., Donaldson, S. S., and Moazed, K.: Posterior ocular abnormalities after irradiation for retinoblastoma. A histopathological study. Br. J. Ophthalmol. 64:660, 1980.

19. Cibis, P. A., Noell, W. K., and Eichel, B.: Ocular effects produced by high-intensity x-radiation. Arch. Ophthalmol. 53:651, 1955.

20. Elmassri, A.: Radiation chorioretinopathy. Br. J. Ophthalmol. 70:326, 1986.

21. Chee, P. H. Y.: Radiation retinopathy. Am. J. Ophthalmol. 66:860, 1968.

22. Bedford, M. A., Bedotto, C., and MacFaul, P. A.: Radiation retinopathy after the application of a cobalt plaque. Report of three cases. Br. J. Ophthalmol. 54:505, 1970.

23. Bagan, S. M., and Hollenhorst, R. W.: Radiation retinopathy after irradiation of intracranial lesions. Am. J. Ophthalmol. 88:694, 1979.

24. Brown, G. C., Shields, J. A., Sanborn, G., Augsburger, J. J., Savino, P. J., and Schatz, N. J.: Radiation retinopathy. Ophthalmology 89:1494, 1982.

25. Thompson, G. M., Migdal, C. S., and Whittle, R. J. M.: Radiation retinopathy following treatment of posterior nasal space carcinoma. Br. J. Ophthalmol. 67:609, 1983.

26. Perrers-Taylor, M., Brinkley, D., and Reynolds, T.: Choroido-retinal damage as a complication of radiotherapy. Acta Radiol. 3:431, 1965.

27. Merriam, G. R., Jr., Szechter, A., and Focht, E. F.: The effects of ionizing radiations on the eye. Front. Radiat. Ther. Oncol. 6:346, 1972.

28. Nakissa, N., Rubin, P., Strohl, R., and Keys, H.: Ocular and orbital complications following radiation therapy of paranasal sinus malignancies and review of literature. Cancer 51:980, 1983.

29. Aristizabal, S., Caldwell, W. L., and Avila, J.: The relationship of time-dose fractionation factors to complications in the treatment of pituitary tumors by irradiation. Int. J. Radiat. Oncol. Biol. Phys. 2:667, 1977.

30. Chacko, D. C.: Considerations in the diagnosis of radiation injury. JAMA 245:1255, 1981.

31. Sanders, J., Sullivan, K., Witherspoon, R., Doney, K., Anasetti, C., Beatty, P., and Petersen, F. B.: Long-term effects and quality of life in children and adults after marrow transplantation. Bone Marrow Transplant. 4(suppl.):27, 1989.

32. Pittillo, R. F., and Lucas, M. B.: Radiosensitization of bacteria by 1-β-D-arabinofuranosylcytosine (NSC-63878). Cancer Chemother. Rep. 51:229, 1967.

33. Iliakis, G., and Bryant, P. E.: Effects of nucleoside analogues α-ara A, β-ara A and β-ara C on cell growth and repair of both potentially lethal damage and DNA double strand breaks in mammalian cells in culture. Anticancer Res. 3:143, 1983.

34. Hiss, E. A., and Preston, R. J.: The effect of cytosine arabinoside on the frequency of single-strand breaks in DNA of mammalian cells following irradiation or chemical treatment. Biochim. Biophys. Acta 478:1, 1977.

35. Phillips, R. A., and Tolmach, L. J.: Repair of potentially lethal damage in x-irradiated HeLa cells. Radiat. Res. 29:413, 1966.

36. Ahnstrom, G., and Erixon, K.: Radiation-in-

duced strand breakage in DNA from mammalian cells. Strand separation in alkaline solution. Int. J. Radiat. Biol. 23:285, 1973.

37. Coleman, C. N., Bump, E. A., and Kramer, R. A.: Chemical modifiers of cancer treatment. J. Clin. Oncol. 6:709, 1988.

38. Mitchell, J. B., and Russo, A.: The role of glutathione in radiation and drug-induced cytotoxicity. Br. J. Cancer. 8(suppl.):96, 1987.

39. Frankenberg, D., and Frankenberg-Schwager, M.: Interpretation of the shoulder of the dose-response curves with immediate plating in terms of repair of potentially lethal lesions during a restricted time period. Int. J. Radiat. Biol. 39:617, 1981.

40. Steel, G. G., and Peckham, M. J.: Exploitable mechanisms in combined radiotherapy-chemotherapy. The concept of additivity. Int. J. Radiat. Oncol. Biol. Phys. 5:85, 1979.

41. Schrecker, A. W., Smith, R. G., and Gallo, R. C.: Comparative inhibition of purified DNA polymerases from murine leukemia virus and human lymphocytes by 1-β-D-arabinofuranosylcytosine-5′-triphosphate. Cancer Res. 34:286, 1974.

42. Yoshida, S., Yamada, M., and Masaki, S.: Inhibition of DNA polymerase-α and β of calf thymus by 1-β-D arabinofuranosylcytosine-5′-triphosphate. Biochim. Biophys. Acta 477:144, 1977.

43. Diabetic Retinopathy Study Research Group: Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. Arch. Ophthalmol. 97:654, 1979.

44. Kinyoun, J. L., Chittum, M. E., and Wells, C. G.: Photocoagulation treatment of radiation retinopathy. Am. J. Ophthalmol. 105:470, 1988.

45. Chaudhuri, P. R., Austin, D. J., and Rosenthal, A. R.: Treatment of radiation retinopathy. Br. J. Ophthalmol. 65:623, 1981.

OPHTHALMIC MINIATURE

Anthony walked over to the bed while the doctor spoke to the nurse, and looked at the body. The eyes were open but unseeing; he gazed into them, and went on gazing. Here perhaps, could he reach it, the secret lay; he leaned closer, seeking, half-unconsiously, to penetrate it. For a moment he could have fancied that they flicked into life, but not common life; that a dangerous vitality threatened him.

Charles Williams, *The Place of the Lion*
Grand Rapids, William B. Eerdmans Publishing Co., 1933, p. 111–112

Pathologic Features of Surgically Excised Subretinal Neovascular Membranes in Age-related Macular Degeneration

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The histopathologic features of ten consecutive surgically excised subfoveal neovascular membranes from patients with age-related macular degeneration were examined. Ultrastructural features included the following in decreasing order of frequency: endothelium-lined vascular channels, new collagen, fibrocytes, retinal pigment epithelium, erythrocytes, and myofibroblasts. Chronic inflammatory cells were frequently evident and included macrophages, lymphocytes, and plasma cells. Basal laminar deposit or diffuse drusen were observed in six of the membranes. Photoreceptors and Bruch's membrane were each observed in three of the specimens, but were not associated with decreased postoperative visual acuity. Fibrin was observed in eight membranes, either within the stroma of the membrane or in association with subretinal hemorrhage.

ADVANCES IN VITREORETINAL microsurgical instrumentation and techniques have provided new direct surgical approaches for the excision of subretinal neovascular membranes in both age-related macular degeneration[1] and in the ocular histoplasmosis syndrome.[2] Clinicopathologic correlation of these cases has thus far been limited to light-microscopic examination of two surgically excised subretinal neovascular membranes, one from a patient with age-related macular degeneration[1] and another from a patient with ocular histoplasmosis syndrome.[2]

Recently, we surgically excised ten consecutive subfoveal neovascular membranes from patients with age-related macular degeneration.[3] Evaluation of ultrastructural features of these specimens has provided new insight regarding the in vivo evolution of subretinal neovascular membranes in age-related macular degeneration.

Material and Methods

Surgical removal of recently symptomatic subfoveal neovascular membranes associated with age-related macular degeneration was performed in ten consecutive patients. The clinical features of the patients, surgical indications, and techniques used have been described.[3]

Excised subretinal neovascular membranes were promptly fixed in 2.5% glutaraldehyde and after two hours were postfixed with 0.1M cacodylate buffer and 1% osmium tetroxide. After standard dehydration, the specimens were embedded in epoxy resin. Semithin (1.0 μm) sections were cut and stained with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead citrate for transmission electron microscopy. Nine of the ten surgically excised subretinal neovascular membranes were available for complete ultrastructural ex-

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amination. One of the ten specimens was partially degenerated and was subjected to a limited ultrastructural analysis. Previously published criteria were used for ultrastructural identification of cells including retinal pigment epithelium, fibrocytes, macrophages, and myofibroblasts, and extracellular material including basal laminar deposit, drusen, Bruch's membrane, collagen, and fibrin.[4-7]

Results

We analyzed the pathologic findings (Table). Surgically excised subretinal neovascularization was characterized by fibrovascular membranes with endothelium-lined vascular channels in all ten (100%) of the specimens (Fig. 1). The vascular channels were composed of endothelium-lined capillaries surrounded by pericytes and were often surrounded by retinal pigment epithelial cells with thickened, multilaminar basement membrane (Fig. 2). The principal cellular constituents in the stroma of the surgically excised membranes were retinal pigment epithelium (Fig. 3) and fibrocytes. One or both of these cell types could be identified in eight of the ten (80%) excised membranes. Six of these eight membranes (75%) contained both cell types. Myofibroblasts were detected in the stroma of a subretinal neovascular membrane in one patient. Chronic inflammatory cells were commonly observed in the membranes. Macrophages were detected most frequently and were found in eight of the ten (80%) specimens. Other inflammatory cells were also sometimes identified in association with the macrophages including lymphocytes and plasma cells. The finding of chronic inflammatory cells did not correlate with previous laser photocoagulation of the subretinal membranes. Polymorphonuclear leukocytes were not detected. Photoreceptor cells or their fragments were identified in three of the ten (30%) membranes (Fig. 4). Phagocytosis of photoreceptor cells by macrophages was sometimes observed (Fig. 5). The finding of photoreceptor cells within the specimens did not correlate with a worsened visual acuity prognosis. The median postoperative visual acuity of patients with photoreceptor cells found in the specimen was 20/350, similar to that of the remaining patients. The worst immediate postoperative visual acuity of a patient with photoreceptor cells in the specimen was 20/400. Basal laminar deposit, located mostly between the retinal pigment epithelium and the inner collagenous layer of Bruch's membrane, was detected in six of the ten (60%) membranes (Fig. 6). Phagocytosis of basal laminar deposit by macrophages was observed in one membrane (Fig. 7). New collagen formation was identified in eight of the ten membranes (80%). Native (old) collagen was observed in three of the ten (30%) specimens. The visual prognosis did not correlate with the detection of either collagen type. Portions of Bruch's membrane were observed in three of the ten (30%) specimens (Figs. 1 and 7). These portions consisted of thickened inner aspects of Bruch's membrane. The visual prognosis in patients with this pathologic finding was similar to that of patients without this feature. Fibrin was detected in eight of the ten (80%) membranes. Generally, the following two types of fibrin distribution were noted: (1) fibrin-enmeshed erythrocytes forming a subretinal clot that was attached to a margin of the subretinal neovascular membrane, often associated with phagocytosis of the fibrin by macrophages (Fig. 8); or (2) fibrin within the fibrous stroma of the membrane.

TABLE
ULTRASTRUCTURAL FEATURES OF TEN SURGICALLY EXCISED SUBRETINAL NEOVASCULAR MEMBRANES IN AGE-RELATED MACULAR DEGENERATION

FEATURE	NO. WITH FEATURE
Cell type	
Endothelium-lined vascular channel	10 of 10
Macrophage	8 of 10
Fibrocyte	6 of 10
Retinal pigment epithelium	6 of 10
Erythrocyte	4 of 10
Lymphocyte	3 of 10
Photoreceptor	3 of 10
Myofibroblast	1 of 10
Plasma cell	1 of 10
Collagen type	
New	8 of 10
Old	3 of 10
Other	
Fibrin	8 of 10
Basal laminar deposit	6 of 10
Bruch's membrane	3 of 10

Discussion

The pathologic features of subretinal neovascularization in age-related macular degenera-

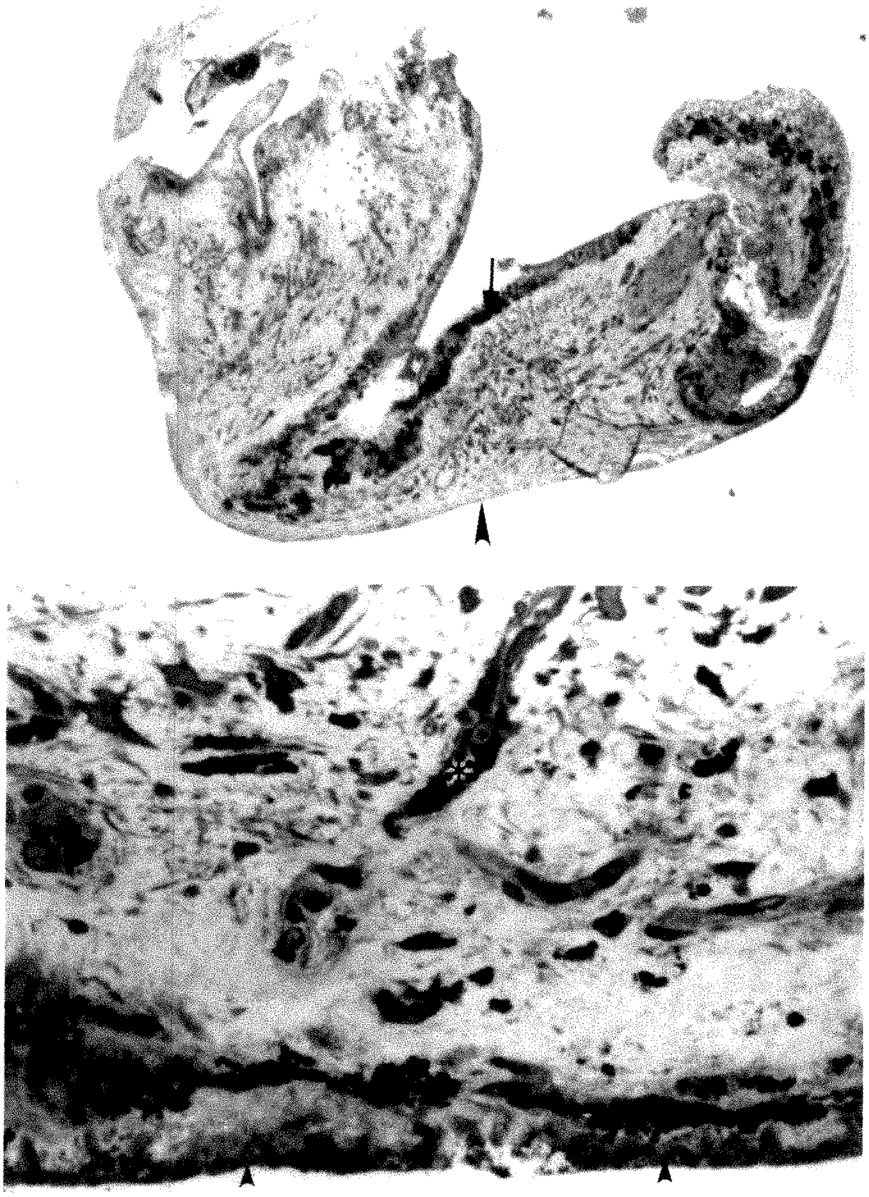

Fig. 1 (Lopez and associates). Top, Fibrovascular subretinal membrane located between inner aspect of Bruch's membrane (arrowhead) and probable retinal pigment epithelium (arrow; toluidine blue, × 10). Bottom, Higher magnification demonstrates inner aspect of Bruch's membrane (arrowheads) and overlying endothelium-lined vascular channels (asterisk) within a fibrocellular stroma (toluidine blue, × 160).

tion have been well-studied in surgical and autopsy eyes.[5,8-11] Data obtained from these previous studies have often been limited to late stages in the evolution of the membranes; however, several animal models have been created to examine the early development of subretinal neovascularization.[12-16] No reproducible animal model of age-related macular degeneration currently exists. Examination of surgically excised subretinal neovascular membranes from patients with age-related macular degeneration provides potential insight regarding the pathogenesis and clinicopathologic features of the membranes.

The surgically excised membranes in the patients in our study were characterized by fibrovascular membranes with endothelium-lined vascular channels. These endothelium-lined vascular channels were of two types. Some vascular channels were composed solely of endothelial cells and pericytes. Other vascular channels were surrounded by palisading retinal pigment epithelium associated with thickened multilaminar basement membrane.

The surgically excised subretinal neovascular membranes demonstrated marked heterogeneity during preoperative fluorescein angiography. Some areas of a subretinal neovascular membrane demonstrated well-defined choroidal neovascularization and other areas were

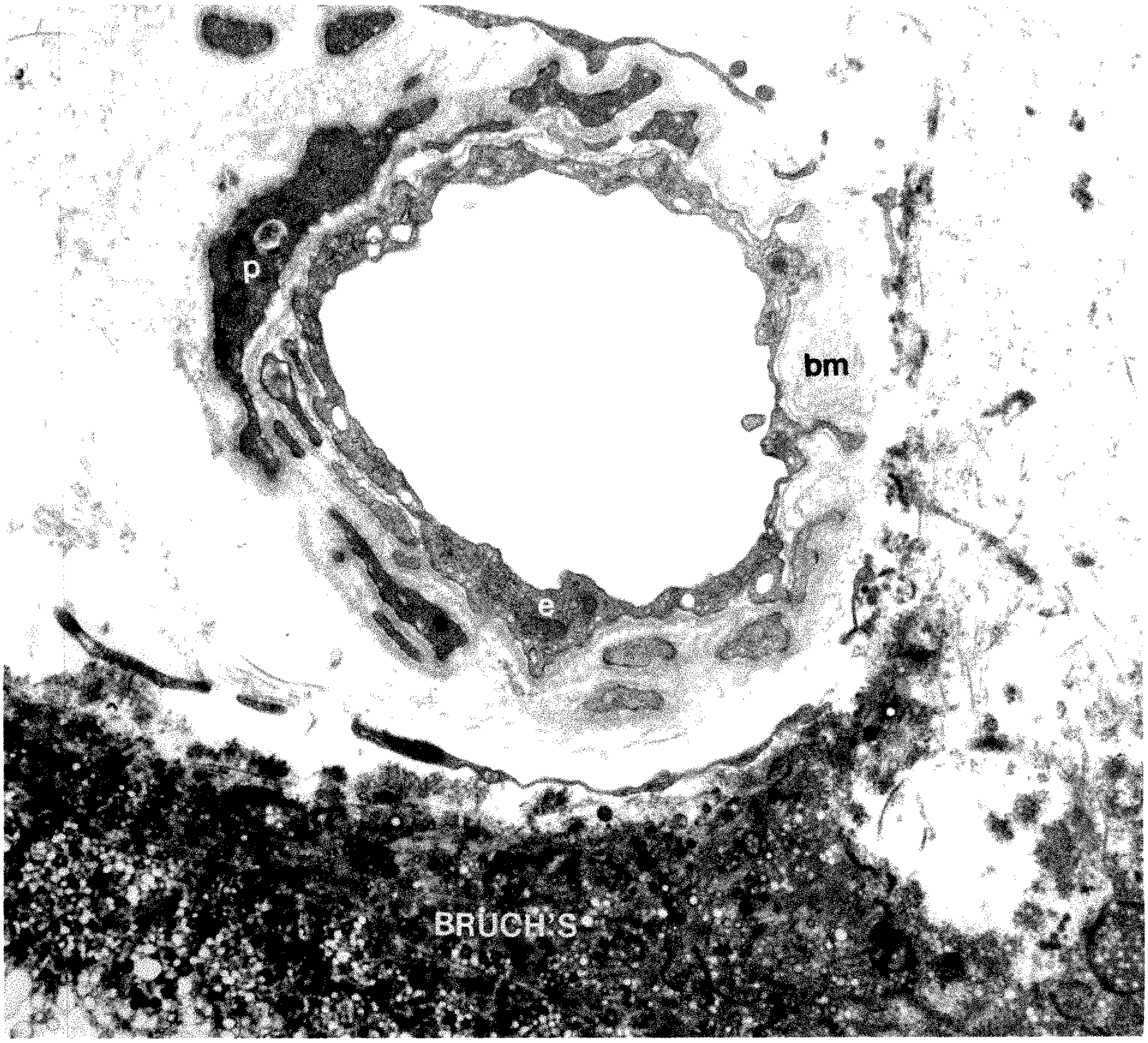

Fig. 2 (Lopez and associates). Same case as that in Figure 1. A dilated vascular channel lined by endothelial cells (e), a pericyte (p), and other cellular processes and multilaminar basement membrane (bm) are shown internal to a portion of a diffusely thickened inner aspect of Bruch's membrane (x 11,160).

associated with poorly defined or undetected choroidal neovascularization. Although exact clinicopathologic correlation of these areas was not possible because of lack of orientation of the specimens, the histopathologic findings noted previously are similar to those described in the evolution of experimental laser-induced subretinal neovascular membranes in primates. In the primate model, initially leaking subretinal neovascular channels composed of endothelial cells and pericytes eventually transformed into nonleaking neovascular channels by the growth of ensheathing retinal pigment epithelium.[14,17,18] This may be an important homeostatic mechanism to allow restoration of the outer blood-retinal barrier and may explain the angiographic heterogeneity of subretinal neovascular membranes.[17] Our findings support the concept of subretinal neovascularization as a common pathologic reaction pattern that has been phylogenetically conserved in a variety of mammalian species and validates the use of

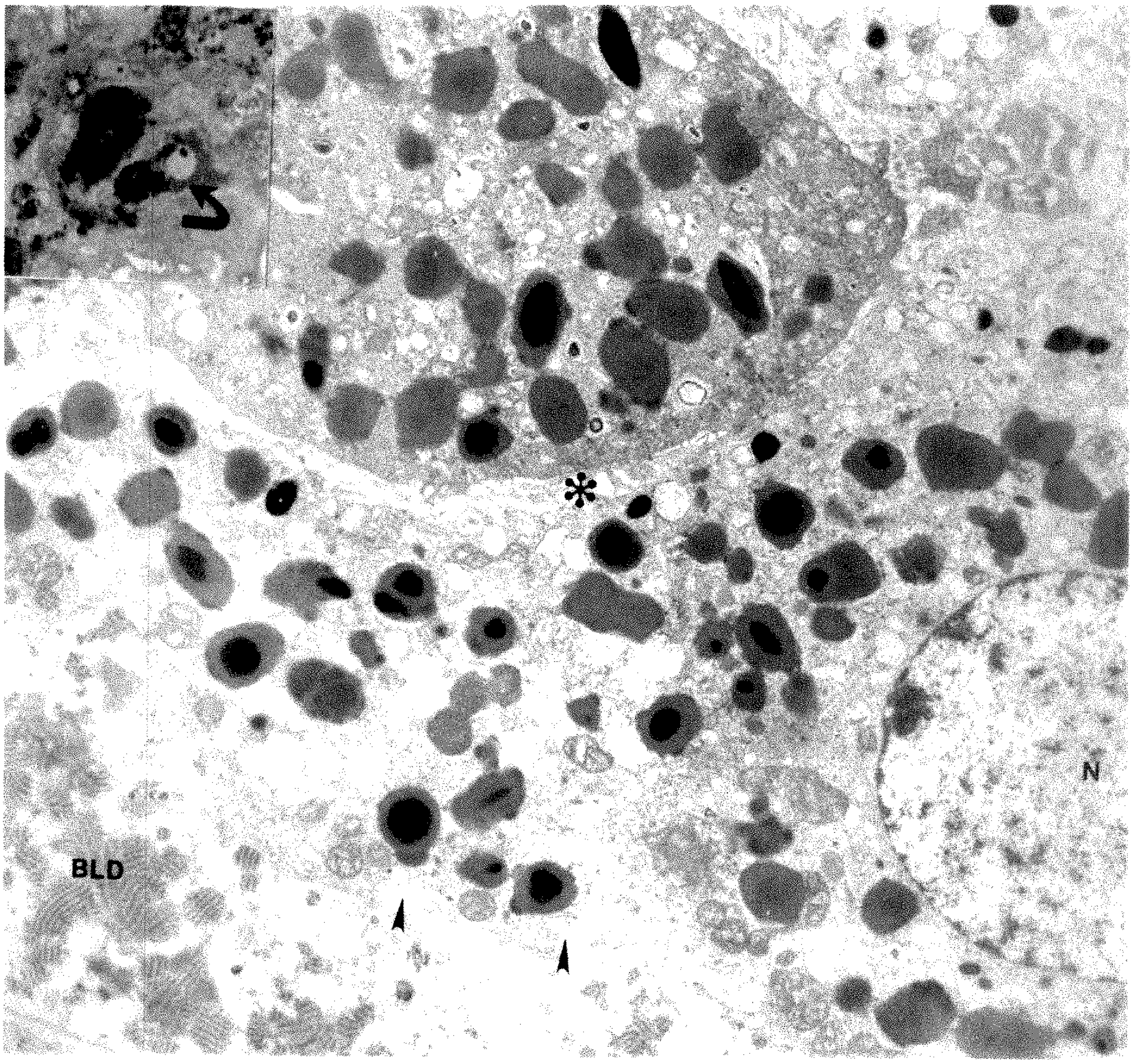

Fig. 3 (Lopez and associates). Retinal pigment epithelial cells in the membrane forming tubuloacinar structure (inset, curved arrow; × 8,990); ultrastructural characteristics of retinal pigment epithelial cell in the membrane including basement membrane production (arrowheads); intracytoplasmic melanin/melanolipofuscin/lipofuscin granules; polarity with apical microvilli (asterisk); and a large, basal round nucleus (N). Basal laminar deposit (BLD) is shown underlying the cell (toluidine blue, original magnification × 160).

experimental animal models to understand better the evolution of subretinal neovascularization in humans.[12,15,16]

Other cellular constituents of surgically excised subretinal neovascular membranes in age-related macular degeneration are consistent with previously reported findings in autopsy and surgically enucleated eyes with age-related macular degeneration.[1,5-11] These constituents include retinal pigment epithelium cells, fibrocytes, myofibroblasts, chronic inflammatory cells, and new collagen formation in the membranes. Myofibroblasts have been associated with contraction of subretinal neovascular membranes and the formation of retinal pigment epithelium tears.[11] Additionally,

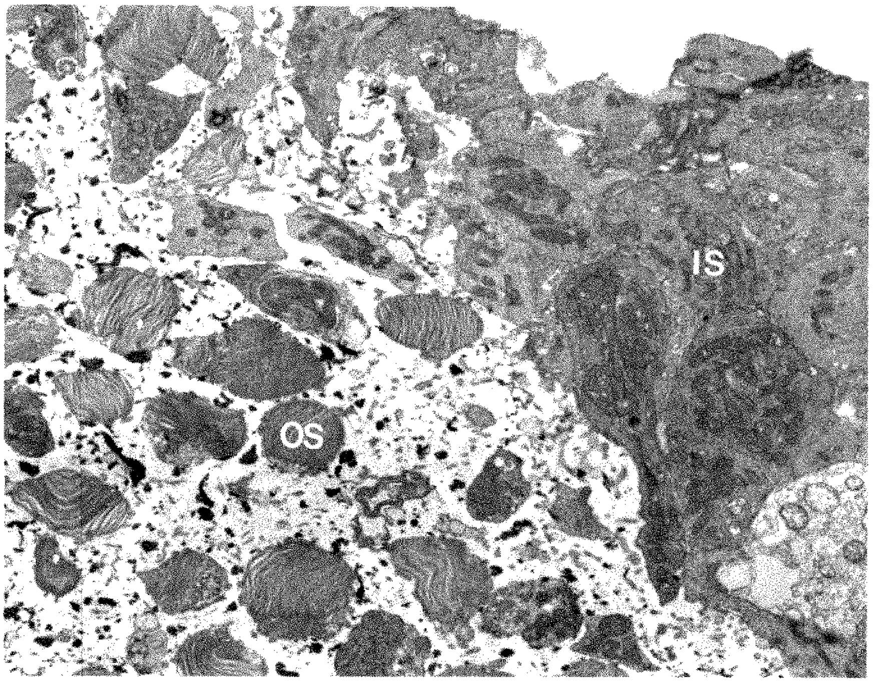

Fig. 4 (Lopez and associates). Cluster of inner segments (IS) and loosely arranged outer segments (OS) of photoreceptor cells in membrane (x 5,320).

scar contraction induced by myofibroblasts within subretinal neovascular membranes may lead to the formation of new breaks in Bruch's membrane and result in the spontaneous growth of subretinal neovascularization.[19]

Chronic inflammatory cells, particularly macrophages, were commonly found in the neovascular membranes whether or not previous laser photocoagulation had been applied. Our findings plus the frequent detection of chronic inflammatory cells at autopsy in human eyes with age-related macular degeneration and in animal models of experimental subretinal neovascularization suggest that these cells may have an important pathogenetic role.[19-21]

Photoreceptor cell fragments, segments of Bruch's membrane and native (old) collagen that may have been derived from surgical de-

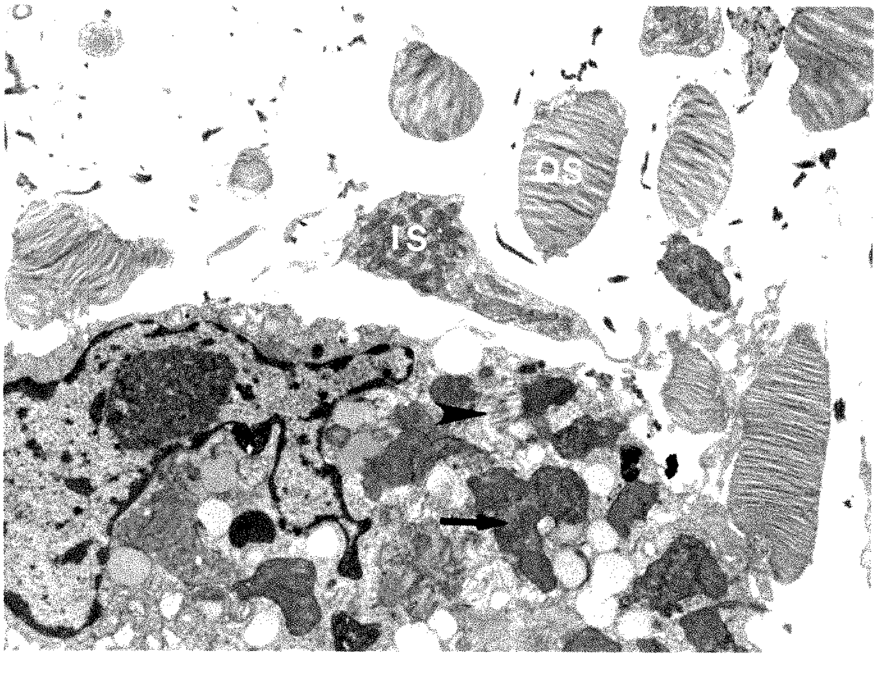

Fig. 5 (Lopez and associates). Inner segments (IS) and outer segments (OS) of photoreceptor cells in membrane in vicinity of macrophage that has phagocytized inner segments (arrow) and outer segments (arrowhead; × 6,080).

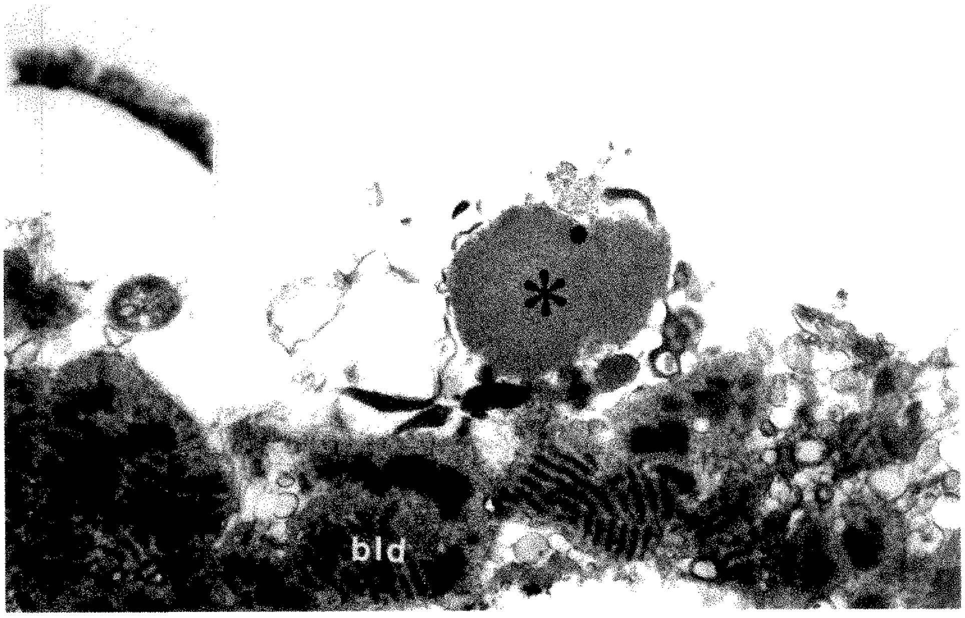

Fig. 6 (Lopez and associates). Fragments of granular material (inset; toluidine blue, × 250) in several membranes were composed of basal laminar deposit (bld) and homogeneous material (asterisk) consistent with diffuse drusen (x 13,440).

lamination of the inner collagenous portion of Bruch's membrane were found in three of the ten (30%) membranes. Surgical removal of these densely adherent structures was unavoidable and even resulted in macular hole formation in one patient. None of these findings could be correlated with a worsened visual acuity prognosis, either because the fragments were removed from visually nonfunctional areas or because the small amount of the excised structures was visually unimportant.

Basal laminar deposit[7-9] or diffuse drusen[8,9] within Bruch's membrane is considered to be a precursor of age-related macular degeneration. Progressive diffuse accumulation of basal laminar deposit on the basal side of the retinal pigment epithelium within the macular area is associated with progressive degeneration of the pigment epithelium[8,9,22] and probably predisposes to the separation of the pigment epithelium and its basement membrane from the remainder of Bruch's membrane.[10,11] Eventually, this diffuse injury may result in a reparative choroidal fibrovascular ingrowth (subretinal neovascularization) that in itself may lead to further pathologic changes such as subretinal hemorrhage, causing acute worsening of vision.[8-11,19,22] Basal laminar deposit ultrastructurally primarily consists of aggregates of wide-spaced collagen having a characteristic banded pattern of approximately 120 nm.[7] Recently, these deposits have been shown to be similar, if not identical, to type-III fibrous wide-spaced collagen that is also found in other intraocular locations and nonocular tissue.[7] In unaffected individuals, basal laminar deposit is distributed in two ultrastructural locations within Bruch's membrane according to age.[7] Basal laminar deposit may be located between the basement membrane of the choriocapillaris endothelium and the outer collagenous zone of Bruch's membrane in most unaffected individuals over 19 years old.[7] Basal laminar deposit between the retinal pigment epithelium and its basement membrane may be of greater pathologic importance and was not found in unaffected individuals until the eighth decade.[7] Premature dysfunction of the retinal pigment epithelium or deposition of basal laminar deposit, or both, may result in the development and evolution of the sequelae of age-related macular degeneration.

Basal laminar deposit, generally located between the basal aspect of the retinal pigment epithelium and the inner collagenous portion of Bruch's membrane, was present in six of the ten (60%) membranes in our study. Absence of the area between the outer collagenous zone of Bruch's membrane and the choriocapillaris in our surgical specimens precluded evaluation

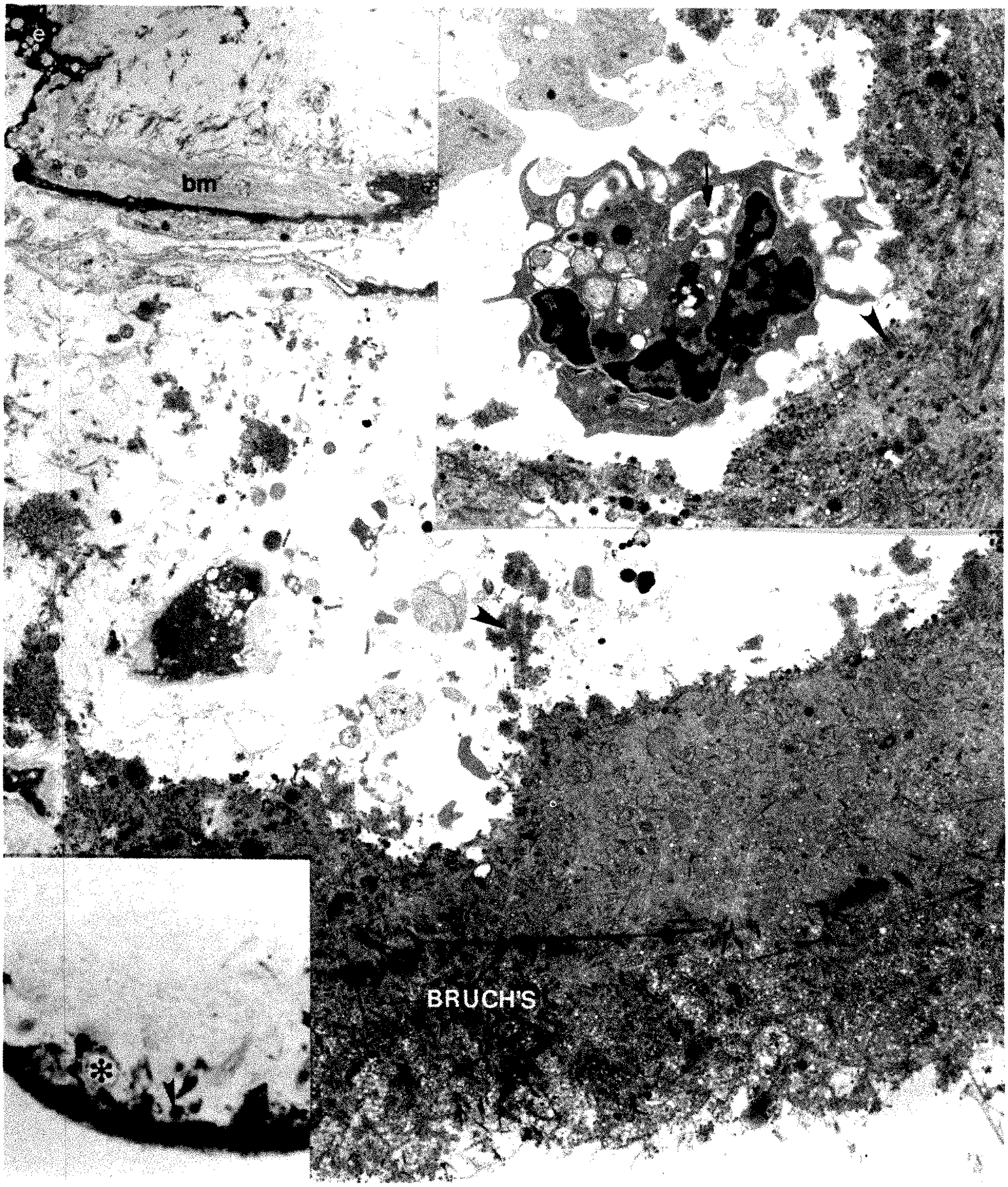

Fig. 7 (Lopez and associates). Vascular channel (lower inset, asterisk; toluidine blue, original magnification × 160), internal to a portion of diffusely thickened inner aspect of Bruch's membrane, is lined by endothelium (e) and surrounded by multilaminar basement membrane (bm). Fragments of basal laminar deposit (arrowheads) are shown in the membrane (original magnification × 5,320). Some of the deposit has been phagocytized by a macrophage (upper inset, arrow; original magnification × 8,120).

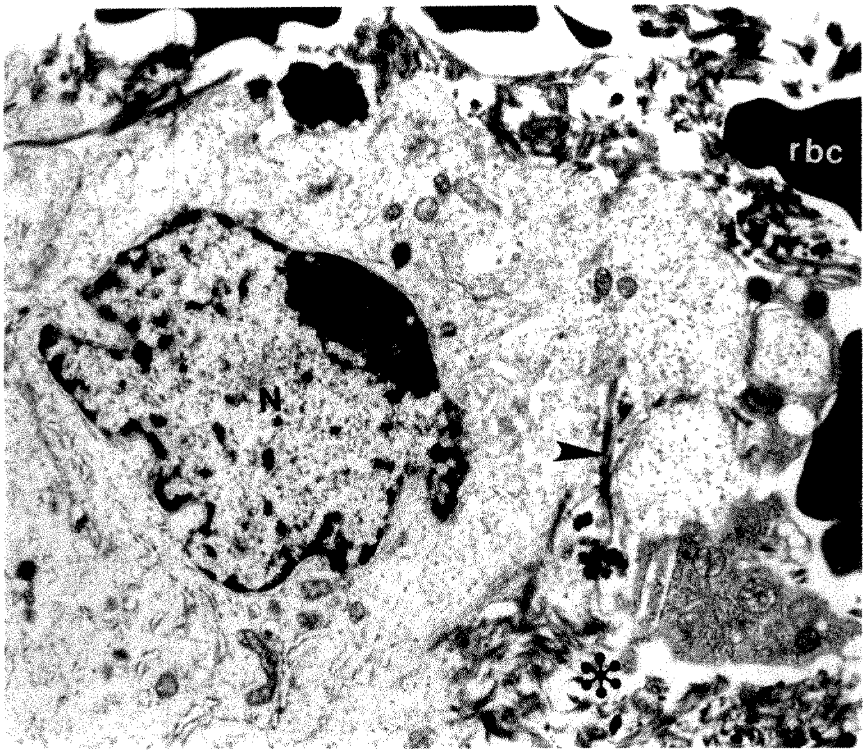

Fig. 8 (Lopez and associates). Macrophage with centrally located nucleus (N) is surrounded by erythrocytes (rbc) and fibrin (asterisk), some of which have been engulfed by the macrophage (arrowhead; × 8,120).

for basal laminar deposit in this location. In one patient, phagocytosis of basal laminar deposit from the inner collagenous portion of Bruch's membrane (Fig. 7) by macrophages suggested this as a physiologic mechanism of drusen resorption after subretinal neovascularization. This may in part explain the frequent occurrence and physiologic function of macrophages and other chronic inflammatory cells within subretinal neovascular membranes in age-related macular degeneration.[19-21]

Fibrin was observed in eight of the ten (80%) surgically excised subretinal neovascular membranes. Generally, two types of fibrin distribution were detected. In one type, erythrocytes associated and enmeshed with fibrin formed a subretinal clot that was adherent to an edge of a subretinal neovascular membrane. In most of these specimens, subretinal hemorrhage occurred preoperatively and no intraoperative hemorrhage occurred before the extraction of the subretinal membrane. In one specimen the excised hemorrhage was formed during removal of the subretinal neovascular membrane and occurred at the bed of the membrane. Phagocytosis of subretinal fibrin and the associated clot by macrophages was observed (Fig. 8). This finding suggests that macrophages may have an important physiologic role in the resorption of subretinal fibrin and hemorrhage associated with subretinal neovascularization.[23] Additionally, these findings support the validity of recent experimental models and new approaches to treatment of massive subretinal hemorrhage secondary to subretinal neovascularization associated with age-related macular degeneration, the use of subretinal tissue plasminogen activator in particular.[23-27] In the other type of fibrin deposition, the fibrin was located within the fibrous stroma of the membrane. In these specimens the fibrin was usually distributed diffusely or in a multilaminar fashion throughout the fibrous stroma of the membranes. The deposition of fibrin in configurations resembling sheets may have served as a scaffold or matrix for the fibrocellular proliferation that formed the stroma of the membrane. Contraction of myofibroblasts attached to either fibrin or collagen within these membranes may partially result in adjacent retinal pigment epithelium tears[10,11] or new breaks in Bruch's membrane at the margins of the subretinal neovascular membrane.[19] New breaks in Bruch's membrane might result in new cycles of reparative choroidal fibrovascular ingrowth (subretinal neovascularization).

Our findings are consistent with the concept of subretinal neovascularization originating from a diffusely thickened inner aspect of Bruch's membrane. Vascular leakage or hemorrhage, or both, may result in fibrin deposition that could act as a scaffold for the membrane. Fibrocytes, perhaps introduced through a defect in Bruch's membrane, may have produced new collagen. Retinal pigment epithelium may migrate to within the membrane and serve a reparative process by sealing off leaky vascular channels. Surgical removal of the membrane can be accomplished in selected cases without removal of underlying choroidal structures and with minimal retinal damage.

References

1. de Juan, E., Jr., and Machemer, R.: Vitreous surgery for hemorrhagic and fibrous complications of age-related macular degeneration. Am. J. Ophthalmol. 105:25, 1988.
2. Thomas, M. A., and Kaplan, H. J.: Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome. Am. J. Ophthalmol. 111:1, 1991.
3. Lambert, H. M., Capone, A., Jr., Aaberg, T. M., Sternberg, P., Jr., and Lopez, P. F.: Surgically excised subretinal neovascular membranes in age-related macular degeneration. Clinical features and techniques. Am. J. Ophthalmol. 112:XXX, 1991.
4. Hogan, M. J., Alvarado, J. A., and Weddell, J. E.: Histology of Human Eye. Philadelphia, W. B. Saunders Co., 1971, pp. 328–363, 424–444.
5. Green, W. R.: Retina. In Spencer, W. H. (ed.): Ophthalmic Pathology. An Atlas and Textbook. Philadelphia, W. B. Saunders Co., 1985, pp. 589–1291.
6. Smiddy, W. E., Green, W. R., Michels, R. G., and de la Cruz, Z.: Ultrastructural studies of vitreomacular traction syndrome. Am. J. Ophthalmol. 107:177, 1989.
7. van der Schaft, T. L., de Bruijn, W. C., Mooy, C. M., Ketelaars, D. A. M., and de Jong, P. T. V. M.: Is basal laminar deposit unique for age-related macular degeneration? Arch. Ophthalmol. 109:420, 1991.
8. Sarks, S.: New vessel formation beneath the retinal pigment epithelium in senile eyes. Br. J. Ophthalmol. 57:951, 1973.
9. ———: Aging and degeneration in the macular region. A clinico-pathologic study. Br. J. Ophthalmol. 60:324, 1976.
10. Green, W. R., and Key, S. N., III: Senile macular degeneration. A histopathologic study. Trans. Am. Ophthalmol. Soc. 75:180, 1977.
11. Green, W. R., McDonnell, P. J., and Yeo, J. H.: Pathologic features of senile macular degeneration. Ophthalmology 92:615, 1985.
12. Ryan, S. J.: The development of an experimental model of subretinal neovascularization in disciform macular degeneration. Trans. Am. Ophthalmol. Soc. 77:707, 1979.
13. Ryan, S. J.: Subretinal neovascularization. Natural history of an experimental model. Arch. Ophthalmol. 100:1804, 1982.
14. Miller, H., Miller, B., Ishibashi, T., and Ryan, S. J.: Pathogenesis of laser-induced choroidal subretinal neovascularization. Invest. Ophthalmol. Vis. Sci. 31:899, 1990.
15. Archer, D. B., and Gardiner, T. A.: Morphologic, fluorescein angiographic, and light microscopic features of experimental choroidal neovascularization. Am. J. Ophthalmol. 91:297, 1981.
16. Jester, J. V., and Smith, R. E.: Subretinal neovascularization after experimental ocular histoplasmosis in a subhuman primate. Am. J. Ophthalmol. 100:252, 1985.
17. Miller, H., Miller, B., and Ryan, S. J.: The role of the retinal pigment epithelium in the evolution of subretinal neovascularization. Invest. Ophthalmol. Vis. Sci. 27:1644, 1986.
18. Pollack, A., and Korte, G. E.: Repair of retinal pigment epithelium and its relationship with capillary endothelium after krypton laser photocoagulation. Invest. Ophthalmol. Vis. Sci. 31:890, 1990.
19. Lopez, P. F., and Green, W. R.: Peripapillary subretinal neovascularization. A review. Retina, in press.
20. Penfold, P. L., Killingsworth, M., and Sarks, S. H.: An ultrastructural study of the role of leukocytes and fibroblasts in the breakdown of Bruch's membrane. Aust. N.Z. J. Ophthalmol. 12:23, 1984.
21. Penfold, P. L., Killingsworth, M. C., and Sarks, S. H.: Senile macular degeneration. The involvement of immunocompetent cells. Graefes Arch. Clin. Exp. Ophthalmol. 223:69, 1985.
22. Sarks, J. P., Sarks, S. H., and Killingsworth, M. C.: Evolution of geographic atrophy of the retinal pigment epithelium. Eye 2:552, 1988.
23. Glatt, H., and Machemer, R.: Experimental subretinal hemorrhage in rabbits. Am. J. Ophthalmol. 94:762, 1982.
24. Hanscom, T. A., and Diddie, K. R.: Early surgical drainage of macular subretinal hemorrhage. Arch. Ophthalmol. 105:1722, 1987.
25. Slusher, M. M.: Evaluation of submacular hemorrhage. Technique and timing. Vitreoretinal Surg. Technol. 1:2, 1989.
26. Wade, E. C., Flynn, H. W., Jr., Olsen, K. R., Blumenkranz, M. S., and Nicholson, D. H.: Subretinal hemorrhage management by pars plana vitrectomy and internal drainage. Arch. Ophthalmol. 108:973, 1990.
27. Lewis, H., Resnick, S. C., Flannery, J. G., and Straatsma, B. R.: Tissue plasminogen activator treatment of experimental subretinal hemorrhage. Am. J. Ophthalmol. 111:197, 1991.

Corneal Topography for Selective Suture Removal After Penetrating Keratoplasty

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Twenty-nine suture removals from 20 eyes (21 patients) on which penetrating keratoplasty had been performed were analyzed in a nonrandomized consecutive study to evaluate the role of computer-assisted corneal topography in selective suture removal to reduce astigmatism. Topographic guidance for suture removal resulted in a net decrease in refractive and keratometric astigmatism in 21 of the 29 cases. The net reduction in astigmatism averaged 1.4, 0.9, and 1.0 diopters when measured by refraction, keratometry, and topography, respectively. The preliminary choice of sutures to be removed on the basis of refraction, keratometry, and inspection was changed in 20 of the 29 cases when information added by the topographic map was considered. Although many variables of suture removal remain unpredictable, computer-assisted corneal topography is a powerful means of describing corneal power after penetrating keratoplasty and is useful as a guide in selective suture removal for reduction of astigmatism.

CORNEAL ASTIGMATISM is often a problem after penetrating keratoplasty and can compromise results. Excessive astigmatism can be associated with poor uncorrected or best-corrected visual acuity, tear film abnormalities, difficult contact-lens fitting, and asthenopic symptoms.[1] Some of the factors that may contribute to astigmatism are mismatch between donor and host tissues, irregular wound healing, and variations in suture placement and tension.[2] Various suture techniques, including interrupted or combined running and interrupted closure, allow for the selective removal of interrupted sutures, with the goal of reducing astigmatism in the postoperative period.[1-4]

Successful visual rehabilitation therefore depends in part on accurate identification of the interrupted suture or sutures whose removal would most effectively reduce astigmatism. In practice, this involves identifying the steepest corneal hemimeridian and the tight suture responsible for inducing this steepening. The clinician has several commonly available tools for measuring corneal power and curvature, including refraction, retinoscopy, and keratometry. These tools are limited to describing one steep and one flat corneal meridian, a situation that may be particularly misleading in patients undergoing keratoplasty in whom irregular or complex astigmatism is common (Fig. 1). Keratoscopy and photokeratography are more powerful tools than refraction, retinoscopy, and keratometry for assessing corneal curvature by allowing the localization of hemimeridional steepness and flatness.[2] Multiple steep hemimeridians or subtle contour abnormalities, however, cannot always be easily interpreted.[5,6] Recently there has been much interest in computer-assisted videokeratography to assess normal and pathologic corneal topography.[6-12] The ability to map subtle corneal power changes accurately over the entire optical zone and beyond gives computer-assisted corneal topography the potential to become the standard for monitoring changes that develop after an operation.[6,8,13,14]

The purpose of this study was to evaluate the role of computer-assisted videokeratography in selective interrupted suture removal after penetrating keratoplasty for the reduction of graft astigmatism. We used computer-assisted corneal topography on 22 consecutive eyes after penetrating keratoplasty.

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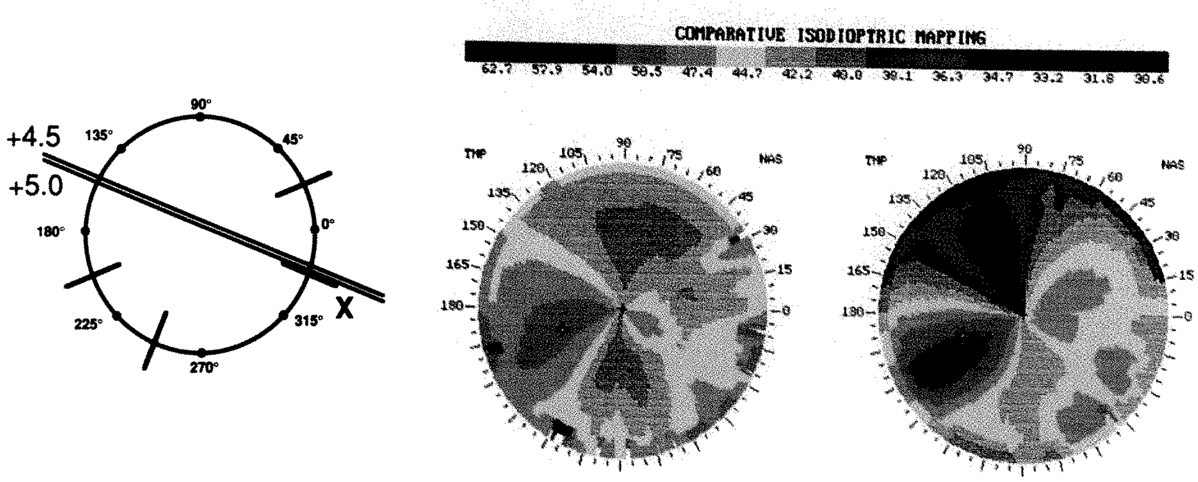

Fig. 1 (Strelow and associates). Diagram and topographic maps from a patient before this study demonstrate the limitation of refraction and keratometry in identifying the steepest meridian. Left, Diagram shows four remaining sutures (short radial lines). The steep meridian by refraction (+4.5 diopters) and keratometry (+5.0 diopters) both indicate removal of the suture near 337 degrees (indicated by the X). This suture was removed. Middle, Topographic map before suture removal. Reliance on this map would have indicated that the steepest hemimeridian corresponds to the suture at 202 degrees. Right, Topographic map four weeks later shows a net increase of 8.9 diopters of astigmatism.

Patients and Methods

Selection of patients—We enrolled 21 patients (22 eyes) between September 1990 and December 1990 who were being monitored after penetrating keratoplasty and who were candidates for selective interrupted suture removal on the basis of excessive residual astigmatism precluding successful spectacle correction. At least

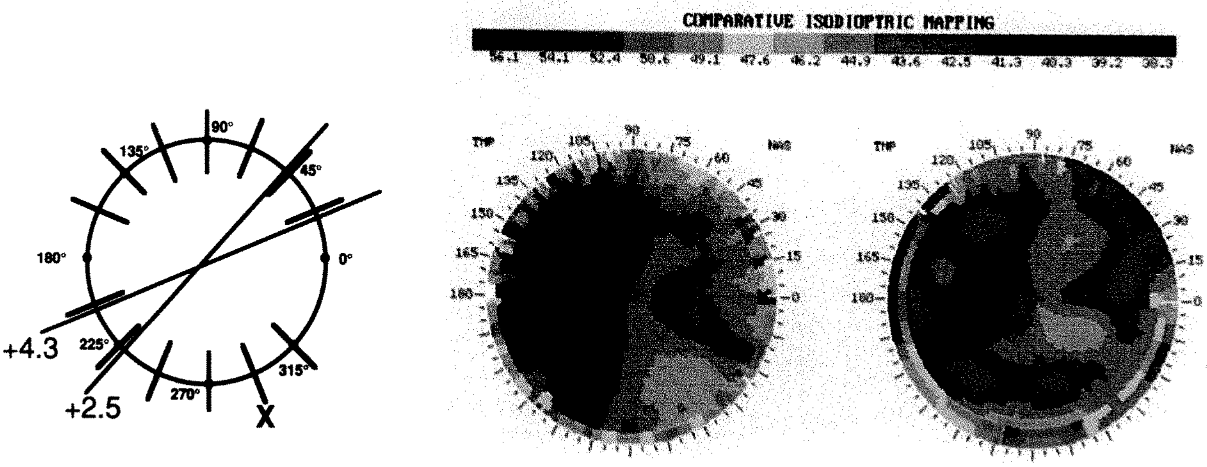

Fig. 2 (Strelow and associates). Diagram and topographic maps demonstrate the utility of topographic guidance for suture removal. Left, Diagram shows 13 remaining sutures. The steep meridians by refraction (+4.3 diopters) and keratometry (+2.5 diopters) identify four possible sutures for removal. The suture removed (indicated by the X) on the basis of the topographic map was not identified by refraction or keratometry. Middle, Topographic map before suture removal demonstrates the flattest and steepest corneal powers along the same meridian. Refraction and keratometry cannot accurately describe this kind of astigmatism. Right, Topographic map three weeks later. The patient had a net reduction of 2.8 diopters of refractive astigmatism and was given spectacles.

four months had elapsed since the operation. Patients whose visual acuities could not be refracted to 20/400 or better and patients with poor topographic images that could not be analyzed by the computer were excluded from enrollment. Continuity of all Placido ring images within the central 4-mm optical zone (eight rings) was required for entry into the study.

Method of examination—A standardized data sheet was compiled on each eye enrolled for each selective suture removal. Surgical history was recorded including indication for penetrating keratoplasty, graft/host trephination diameters, time interval from the operation to suture removal, and suture technique. Careful slit-lamp examination included drawing a schematic cornea with precise localization of all remaining sutures. Manifest refraction (retinoscopy with subjective refinement) and keratometry (Haag-Streit keratometer, Leibefeld, Switzerland) were recorded by one of us (S.S.). The steep meridians as identified by refraction and keratometry, respectively, were used to guide slit-lamp identification of tight sutures, thereby localizing the steep corneal hemimeridian. Tight sutures were identified by visible stress lines in the cornea. The surgeon made a preliminary recording of the one or two sutures to be removed on the basis of clinical data alone (refraction, keratometry, and inspection of sutures). Generally, two sutures were chosen for higher degrees of astigmatism and when refraction and keratometry respectively identified differing steep meridians.

At this point, computer-assisted videokeratography was used to generate a color-coded topographic map for analysis. The steep corneal hemimeridians were readily identified on the topographic map and were compared to the schematic drawing to locate the suture most closely associated with the steep hemimeridians by topography. One or two sutures were then removed on the basis of the topographic map (Fig. 2).

Data were collected on the incidence in which the topographic map analysis resulted in removal of different sutures than had been preliminarily selected on the basis of refraction, keratometry, and inspection of sutures. The information collected by refraction and keratometry was known at the time of topographic analysis, but only sutures correlating with topographic steepness were removed.

Patients were reexamined three to five weeks after suture removal for change in uncorrected and best-corrected spectacle acuity, manifest refraction, keratometry, and corneal topography.

Method of computer-assisted videokeratography—For each suture removal, computer-assisted videokeratography was performed immediately before suture removal and three to five weeks after suture removal by one of us (S.S.). The EyeSys corneal analyzer (Houston, Texas) was used to generate the color-coded topographic maps. This system consisted of the following: (1) a keratoscope that projects Placido rings onto the anterior corneal surface, (2) a real-time video monitoring system to capture the Placido image, and (3) computer-driven programs to digitize the image and analyze the keratograph using proprietary algorithms. The EyeSys corneal analyzer has been shown to be highly reliable and reproducible on healthy corneas.[14]

Topographic maps were then obtained. One drop of artificial tears was instilled onto the cornea to ensure adequate tear film and excessive tear lake was blotted. An eyelid speculum was not used. The patient was instructed to fixate on the central target light on the keratoscope and compliance was checked on the video monitor. The corneal image was properly aligned on the video screen and focused sharply using cross marks projected onto the corneal surface. Two high-quality topographic images were analyzed to ensure reproducibility. High-quality images were judged by absence of excessive tear pooling along the lower eyelid, resulting in image distortion, proper centration, and continuity of all Placido ring images within the central 4-mm optical zone. One topographic image was entered into the computer for processing and was displayed as a color-coded topographic map using the normalized scale. This scale used all 14 colors to describe the specific dioptric range of each cornea. Usually each color step represented a 0.7- to 1.0-diopter power change. The computer program allowed for direct comparison of the topographic maps on the same screen before and after suture removal, using a normalized scale that spanned the specific dioptric range of the two maps. The topographic map was photographed for comparison with the actual suture positions.

Method of astigmatism calculation—We calculated the change in astigmatism caused by su-

TABLE 1
VISUAL ACUITY AND CLINICAL DATA

PATIENT NO.[*]	DIAGNOSIS (ORIGINAL GRAFT INDICATION)	MONTHS AFTER THE OPERATION	NO. OF SUTURES REMOVED	UNCORRECTED VISION		BEST-CORRECTED VISION		CLINICAL SUTURE CHOICE CHANGED BY TOPOGRAPHY
				BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL	BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL	
1	Chandler's syndrome	30	2	20/80	20/200	20/30	20/20	Yes
2	Keratoconus	23	1	20/60	20/60	20/30	20/25	No
3	Graft failure (scar)	11	2	20/100	20/70	20/20	20/15	Yes
4A	Pseudophakic bullous keratopathy	12	1	20/100	20/80	20/100	20/70	Yes
4B	Pseudophakic bullous keratopathy	13	1	20/80	20/70	20/70	20/70	Yes
4C	Pseudophakic bullous keratopathy	14	2	20/70	20/70	20/70	20/50	Yes
5[†]	Fuchs' syndrome	12	1	20/200	20/200	20/40	20/50	No
6A	Fuchs' syndrome	25	2	20/300	20/300	20/70	20/50	Yes
6B	Fuchs' syndrome	26	2	20/300	20/50	20/50	20/50	Yes
7	Pseudophakic bullous keratopathy	51	1	20/800	20/800	20/50	20/25	No
8A[‡]	Keratoconus	11	2	20/60	20/80	20/50	20/40	Yes
8B	Keratoconus	12	2	20/80	20/40	20/40	20/25	Yes
9	Pseudophakic bullous keratopathy	13	1	20/50	20/60	20/40	20/30	No
10	Pseudophakic bullous keratopathy	55	2	20/800	20/800	20/50	20/30	Yes
11	Keratoconus	29	1	20/400	20/400	20/20	20/15	No
12	Interstitial keratitis	12	1	20/50	20/50	20/50	20/40	Yes
13	Keratoconus	49	1	20/80	20/100	20/25	20/20	No
14, R.E.	Pseudophakic bullous keratopathy	41	1	20/800	20/50	20/60	20/50	Yes
14, L.E.	Fuchs' syndrome	16	1	20/100	20/80	20/70	20/70	No
15	Keratoconus	25	1	20/60	20/70	20/30	20/30	Yes
16	Fuchs' syndrome	31	1	20/70	20/70	20/40	20/50	Yes
17	Pseudophakic bullous keratopathy	4	1	20/60	20/70	20/50	20/40	Yes
18A	Fuchs' syndrome	17	2	20/300	20/300	20/60	20/50	No
18B	Fuchs' syndrome	18	2	20/300	20/80	20/50	20/50	Yes
18C	Fuchs' syndrome	18	2	20/80	20/400	20/50	20/80	Yes
18D	Fuchs' syndrome	19	1	20/400	20/400	20/80	20/60	No
18E	Fuchs' syndrome	19	2	20/400	20/200	20/60	20/40	Yes
19	Fuchs' syndrome	31	1	20/80	20/30	20/30	20/30	Yes
20	Graft failure (ulcer)	11	1	20/200	20/100	20/50	20/40	Yes
21A	Graft failure (pseudophakic bullous keratopathy)	11	2	20/80	20/100	20/50	20/50	No
21B[‡]	Graft failure (pseudophakic bullous keratopathy)	12	1	20/100	20/100	20/50	20/50	Yes

[*] A,B,C,D,E indicate separate suture removals in the same eye.

[†] Not included in data analysis.

[‡] Combined running/interrupted suture technique used in Patient 8.

TABLE 2
ASTIGMATISM BEFORE AND AFTER SUTURE REMOVAL

PATIENT NO.[*]	REFRACTIVE ASTIGMATISM (DIOPTERS)		KERATOMETRIC ASTIGMATISM (DIOPTERS)		TOPOGRAPHIC ASTIGMATISM (DIOPTERS)		SUTURE INDUCED TOPOGRAPHIC POWER (DIOPTERS)[†]	
	BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL	BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL	BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL	BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL
1	3.3	4.0	0.5	3.0	4.5	4.6	—	—
2	5.8	4.0	13.5	11.0	9.6	12.3	49.7	50.5
3	3.5	1.3	4.5	1.5	5.0	1.8	—	—
4A	2.5	3.0	2.5	5.0	10.0	6.5	46.4	46.0
4B	3.0	3.8	5.0	1.0	6.5	5.8	48.9	42.7
4C	3.8	1.5	1.0	3.5	5.8	4.1	—	—
5[‡]	7.5	6.3	8.5	NA	9.7	NA	46.9	NA
6A	7.0	6.0	6.0	15.5	6.6	9.9	—	—
6B	6.0	0.0	15.5	13.0	9.9	13.1	—	—
7	5.0	2.5	3.0	3.0	7.0	3.1	51.8	47.3
8A[§]	3.5	1.5	7.0	5.0	3.8	6.9	—	—
8B	1.5	2.5	5.0	1.0	6.9	2.2	—	—
9	5.0	1.8	7.5	4.0	8.6	5.8	46.7	46.4
10	5.0	9.5	4.0	9.0	6.3	5.3	—	—
11	3.8	3.0	5.5	3.5	6.3	3.5	46.6	46.2
12	5.0	0.3	8.0	2.5	9.1	5.5	49.6	44.6
13	6.5	4.5	5.5	4.5	5.0	4.4	46.7	46.9
14, R.E.	7.5	1.8	9.0	3.5	7.9	7.8	47.9	47.7
14, L.E.	4.0	1.0	4.5	1.5	5.3	3.6	43.2	40.4
15	2.8	0.0	2.0	1.3	3.4	2.2	48.1	46.6
16	5.8	7.5	6.5	8.0	12.3	7.8	44.8	42.7
17	1.5	1.5	6.0	3.0	7.6	4.6	50.1	47.7
18A	4.0	3.8	7.5	5.0	7.8	7.5	—	—
18B	3.8	2.5	5.0	1.0	7.5	8.3	—	—
18C	2.5	6.0	1.0	10.0	8.3	10.9	—	—
18D	6.0	4.8	10.0	6.0	10.9	8.2	50.7	47.3
18E	4.8	4.0	6.0	5.0	8.2	7.1	—	—
19	3.5	1.5	2.5	1.0	4.7	4.1	46.8	45.4
20	4.3	1.5	2.5	1.5	3.8	2.2	45.7	45.4
21A	7.5	2.0	5.5	3.0	9.4	9.0	—	—
21B[‡]	2.0	5.0	3.0	NA	9.0	NA	52.0	NA

[*] A,B,C,D,E indicates separate suture removals in the same eye.

[†] Power at the 3-mm optic zone of the steep hemimeridian corresponding to the tight suture removed.

[‡] Not included in data analysis.

[§] Combined running/interrupted suture technique used in Patient 8.

NA indicates data not attainable because of poor epithelial surface.

ture removal in terms of refractive astigmatism, keratometric astigmatism, and topographic astigmatism. The goal of selective suture removal is to move from a more irregular astigmatic contour toward a more regular spherical contour. Therefore, net astigmatic change was calculated for refractive and keratometric astigmatism using simple subtraction of dioptric astigmatism before and after suture removal without regard to axis shift. The change in astigmatism was expressed as a positive (+) value if astigmatism increased and a negative

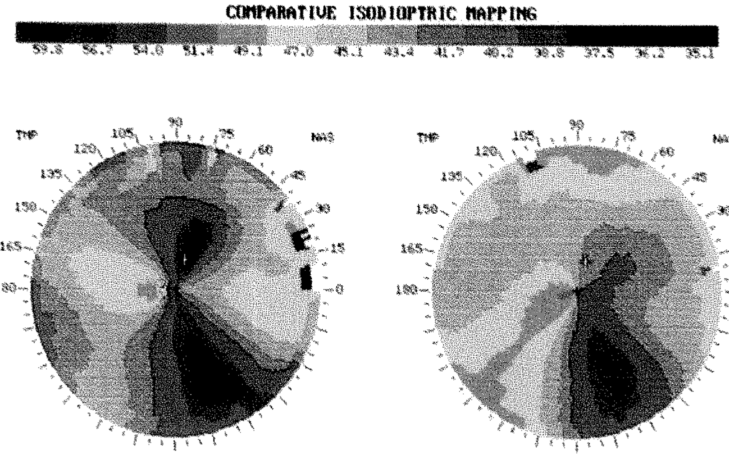

Fig. 3 (Strelow and associates). Topographic maps of the right eye demonstrate that there is less refractive cylinder and better uncorrected visual acuity than might be predicted on the basis of the topographic map. Left, Topographic map before suture removal. The patient had 20/800 uncorrected visual acuity and 7.5 diopters of refractive cylinder. A suture was removed at the 165-degree hemimeridian. Right, Topographic map three weeks later. Uncorrected visual acuity has improved to 20/50 with a net decrease of 5.7 diopters of refractive astigmatism. By topographic measurement, 7.8 diopters of astigmatism remains, but the pattern of residual astigmatism demonstrated by topography apparently does not adversely affect the visual axis.

(−) value if astigmatism decreased. For refractive astigmatism, the difference in plus cylinder was used. For keratometric astigmatism, the dioptric difference between the steep and flat meridians were compared before and after suture removal.

Topographic astigmatism was measured at specific points on the digitized color map to allow a truly hemimeridional assessment of power. Current computer-driven algorithms calculate and diagram the steep and flat meridians in graphic form. These meridians represent the average steepest and average flattest meridians and are not useful for choosing the steepest hemimeridian that corresponds to a specific suture. We chose the dioptric power represented by the data point closest to the 3-mm optical zone at the steepest and flattest hemimeridians. The dioptric difference between these two points represents the topographic astigmatism at the 3-mm optical zone. This method allows for more accurate description of the extremes of corneal power change than do averaging techniques across an entire meridian. This is especially true in irregular astigmatism in which the steep and the flat hemimeridians may line up in the same meridian. The change in topographic astigmatism after suture removal was expressed in diopters as positive (+) if astigmatism increased and negative (−) if astigmatism decreased.

For patients in whom a single suture was removed in the steep hemimeridian, the amount of astigmatism induced by that suture can be directly measured by topography. In this measurement the steep hemimeridian influenced by the tight suture is measured at the 3-mm optical zone before suture removal. The measurement is repeated after suture removal at the same point on the topographic map and simple subtraction will yield the astigmatism induced by the suture.

Method of visual acuity measurement—Standard projected Snellen visual acuity was mea-

TABLE 3

POSTSURGICAL INTERVAL TO SELECTIVE SUTURE REMOVAL

TIME (MONTHS)	NO. OF EYES
4–6	1
7–12	6
13–24	4
25–36	6
37–48	1
≥ 49	3

TABLE 4
EFFECT OF SELECTIVE SUTURE REMOVAL ON ASTIGMATISM (N = 29)

	NO. OF EYES WITH IMPROVED ASTIGMATISM (%)	NO. OF EYES WITH UNCHANGED ASTIGMATISM (%)	NO. OF EYES WITH WORSE ASTIGMATISM (%)
Topographic astigmatism	22 (76%)	0 (0%)	7 (24%)
Keratometric astigmatism	21 (72%)	1 (3%)	7 (24%)
Refractive astigmatism	21 (72%)	1 (3%)	7 (24%)

sured for both uncorrected and best-corrected visual acuity.

Results

Twenty-two eyes from 21 patients encompassing 31 suture removals were entered into the study (Tables 1 and 2). Two patients could not be included for data analysis because of poor keratographic and keratometric mires after suture removal. In both patients, this was caused by epitheliopathy. Best-corrected visual acuity was unchanged in one patient and worse by one line in the other patient three weeks after suture removal. Therefore, data analysis included 21 eyes from 20 patients and 29 suture removals. One patient who underwent suture removal in both eyes was entered into the study. Four patients had more than one suture removal entered.

The predominant surgical technique used was 16 interrupted 10-0 nylon suture closures in 20 eyes. The remaining eye was closed with a continuous 16-bite 10-0 nylon combined with eight interrupted 10-0 nylon sutures. The grafts were oversized 0.2 mm or 0.5 mm in all cases. Indications for penetrating keratoplasty were determined (Table 1). Time intervals between the operation and selective suture removal were also determined (Table 3).

Selective suture removal using topographic guidance resulted in a net decrease in astigmatism in over 70% of cases (22 of 29 cases; Table 4). The net reduction in astigmatism averaged 1.0 ± 2.4, 0.9 ± 3.8, and 1.4 ± 2.5 diopters when measured by topography, keratometry, and refraction, respectively (Table 5). Topographically measured suture-induced astigmatism in the steep hemimeridian decreased an average of 2.1 diopters (range, +0.8 to −7.4 diopters) when a single suture was removed in that hemimeridian.

Topographic guidance for selective suture removal resulted in improvement of either uncorrected or best-corrected visual acuity in 25 of 29 patients (86%). Two of the four remaining patients maintained their same best-corrected visual acuity but with less refractive astigmatism (net decrease of 2.8 and 5.6 diopters, respectively). The two remaining patients (7%) had a net increase (+1.8 and +3.5 diopters) in refractive astigmatism, losing one and three lines of best-corrected visual acuity, respectively, with increased irregular astigmatism.

The preliminary clinical impression (determined on the basis of keratometry, refraction, and inspection) of sutures to be removed was changed in 20 of 29 cases (69%) when the topographic map was considered. No suture was removed without topographic evidence for a corresponding steep hemimeridian. In some cases (nine of 29), topography merely confirmed the clinical choice made by keratometry, refraction, and inspection. In the other cases,

TABLE 5
EFFECT OF SELECTIVE SUTURE REMOVAL ON ASTIGMATISM (N = 29)

	NET REDUCTION IN ASTIGMATISM (DIOPTERS)	STANDARD DEVIATION	RANGE (DIOPTERS)
Topographic astigmatism	− 1.0	± 2.4	+ 3.4 to − 4.8
Keratometric astigmatism	− 0.9	± 3.8	+ 9.5 to − 5.5
Refractive astigmatism	− 1.4	± 2.5	+ 4.5 to − 6.0

TABLE 6
TOPOGRAPHIC SELECTION OF A SINGLE SUTURE FOR REMOVAL

METHOD OF ASTIGMATISM MEASUREMENT	MEAN DECREASE IN ASTIGMATISM IN DIOPTERS (S.D.)	
	CLINICAL CHOICE OF SUTURE CONFIRMED BY TOPOGRAPHY IN 7 EYES	CLINICAL CHOICE OF SUTURE CHANGED BY TOPOGRAPHY IN 9 EYES
Topography	− 1.7 (2.2)	− 2.1 (1.6)
Keratometry	− 2.3 (1.4)	− 1.9 (2.8)
Refraction	− 2.1 (0.9)	− 1.7 (2.6)

however, the topographic map added information that changed the meridian, the hemimeridian, or the number of sutures removed. The effect of topography in changing the clinical choice of which suture to remove may be most directly evaluated in the cases of single suture removal. Reduction of astigmatism when the clinically chosen suture was confirmed by topography was not different as compared to when the clinically chosen suture was changed on the basis of topography. Topographically removed sutures were efficacious in decreasing astigmatism even when keratometry, refraction, and inspection would indicate a different suture (Table 6).

Discussion

Topography has become an integral part of our method of selective suture removal for reduction of astigmatism after penetrating keratoplasty. This study demonstrated the efficacy of using topography to reduce astigmatism by guiding suture removal. Many variables of suture removal still remain unpredictable with a considerable range in the amount of astigmatic change. We were surprised at the number of times a clinical decision to remove a suture based on refraction, keratometry, and inspection of sutures led us to a different suture choice than did topography. This study was not designed to show that topography is better or worse than refraction, keratometry, and inspection in choosing a suture to be removed. Rather, this study was conducted to indicate whether topography could fulfill its theoretical promise to be a standard guide in selective suture removal.

Despite our use of topography, refraction remains essential as the overall indicator of visual acuity function. After keratoplasty, the cornea may be a truly multifocal surface. This can be demonstrated by topography and explains the various refractions often found after penetrating keratoplasty. A multifocal surface can also explain better uncorrected visual acuity or less refractive cylinder than would have been predicted on the basis of the topographic map (Fig. 3). We do not routinely remove sutures in patients with a crisp low cylinder refraction that provides good visual acuity. Our end point is good visual acuity regardless of how astigmatic or irregular the topographic map may appear.

In analyzing our data, it was evident that single suture removal was more efficacious and predictable at decreasing astigmatism than was the removal of multiple sutures at one time. We were unable to make this conclusion, however, because of our inability to separate the confounding variable of preexisting irregular astigmatism. Irregular astigmatism exists when there is variation in corneal curvature along a given meridian or when the intersection of the steep and flat meridians is other than 90 degrees. In this analysis, patients with high degrees of irregular astigmatism were identified when the steep meridional measurements by refraction and keratometry did not correlate with the steep hemimeridians of the topographic map. Patients who had two sutures removed at one time were 2.5 times more likely to have high degrees of preexisting irregular astigmatism than were patients who had only a single suture removed. It may be the degree of preexisting astigmatic irregularity, rather than the dioptric amount of astigmatism or the number of sutures removed, that is more important in the predictability of suture removal to reduce astigmatism.

This study demonstrated that corneal topography using the EyeSys corneal analyzer is a reliable method of analyzing corneal power after penetrating keratoplasty to guide in selective suture removal. The importance of information provided by computerized corneal topography in facilitating visual acuity rehabilitation of patients undergoing penetrating keratoplasty remains to be decided and the superiority of topography over keratography or hand-held keratoscopy is still uncertain. The role of predictably and simultaneously removing multiple sutures and the role of decreasing the time interval between suture removals in speeding rehabilitation also remain uncertain. Some topographic patterns may also predict an unstable wound or increased unpredictability with multiple suture removal. Many questions remain to be addressed in future studies if this new technology is to realize its potential and justify its expense.

References

1. Binder, P. S.: The effect of suture removal on postkeratoplasty astigmatism. Am. J. Ophthalmol. 105:637, 1988.
2. Harris, D. J., Waring, G. O. III, and Burk, L. L.: Keratography as a guide to selective suture removal for the reduction of astigmatism after penetrating keratoplasty. Ophthalmology 96:1597, 1989.
3. Feldman, S. T., and Brown, S. I.: Reduction of astigmatism after keratoplasty. Am. J. Ophthalmol. 103:477, 1987.
4. Burk, L. L., Radjee, B., Waring, G. O. III, and Stulting, R. D.: The effect of selective suture removal on astigmatism following penetrating keratoplasty. Ophthalmic Surg. 19:849, 1988.
5. Klyce, S. D.: Computer-assisted corneal topography. High-resolution graphic presentation and analysis of keratoscopy. Invest. Ophthalmol. Vis. Sci. 25:1426, 1984.
6. Wilson, S. E., and Klyce, S. D.: Advances in the analysis of corneal topography. Surv. Ophthalmol. 35:269, 1991.
7. Bogan, S. J., Waring, G. O. III, Ibrahim, O., Drews, C., and Curtis, L.: Classification on normal corneal topography based on computer-assisted videokeratography. Arch. Ophthalmol. 108:945, 1990.
8. Hannush, S. B., Crawford, S. L., Waring, G. O. III, Gemmill, M. C., Lynn, M. J., and Nizam, A.: Reproducibility of normal corneal power measurements with a keratometer, photokeratoscope, and video imaging system. Arch. Ophthalmol. 108:539, 1990.
9. McDonnell, P. J., Garbus, J., and Lopez, P. F.: Topographic analysis and visual acuity after radial keratotomy. Am. J. Ophthalmol. 106:692, 1988.
10. Wilson, S. E., Lin, D. T. C., Klyce, S. D., Reidy, J. J., and Insler, M. S.: Topographic changes in contact lens-induced corneal warpage. Ophthalmology 97:734, 1990.
11. Lin, D. T. C., Wilson, S. E., Klyce, S. D., and Insler, M. S.: Topographic changes that occur with 10-0 nylon suture removal following penetrating keratoplasty. Refract. Corneal Surg. 6:21, 1990.
12. Lin, D. T. C., Wilson, S. E., Reidy, J. J., Klyce, S. D., McDonald, M. B., Kaufman, H. E., and McNeill, J. I.: An adjustable single running suture technique to reduce post keratoplasty astigmatism. A preliminary report. Ophthalmology 97:934, 1990.
13. Hannush, S. B., Crawford, S. L., Waring, G. O. III, Gemmill, M. C., Lynn, M. J., and Nizam, A.: Accuracy and precision of keratometry, photokeratoscopy, and corneal modeling on calibrated steel balls. Arch. Ophthalmol. 107:1235, 1989.
14. Williams, C. H., Hannush, S. B., Reynolds, D. R., and Menduke, H.: Reproducibility of normal corneal power measurements with a keratometer and a videokeratoscope. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 999.

Developing Entry Criteria for Studies of Severe Postkeratoplasty Astigmatism

John A. Millin, M.D., and Leo J. Maguire, M.D.

Investigators who use keratometry or topography systems to plan operations for the correction of severe postkeratoplasty astigmatism assume the study group is homogeneous. To test this hypothesis, we established four entry criteria we believed were necessary to ensure a homogeneous group. The criteria were as follows: (1) best-corrected or pinhole visual acuity greater than or equal to 20/40; (2) graft well centered relative to the corneal light reflex; (3) corneal light reflex within 0.5 mm of the center of the entrance pupil; and (4) a minimum of ten central keratoscope rings of the Corneal Modeling System accurately digitized. A retrospective analysis of the keratoscope images of 20 consecutive patients (20 eyes) referred for correction of postkeratoplasty astigmatism was performed to determine the percentage of patients who met the proposed criteria. Only seven (35%) simultaneously met all four entry criteria. Investigators interested in comparing techniques to correct this problem are faced with a dilemma. Strict entry criteria will ensure a homogeneous study group but will exclude most patients. More lenient entry criteria will increase the number of eligible subjects but will introduce heterogeneity, which may confound results.

MOST STUDIES of transverse keratotomy for the correction of severe postkeratoplasty astigmatism use a keratometer to determine the amount of corneal astigmatism and the location of the steep axis.[1,2] Once that information is obtained, the center of the graft is marked, the steep axis identified, and an algorithm is used to determine the parameters of incision necessary to correct the astigmatism. This method assumes the center of the keratometer mire is located at the center of the graft. The location of the keratometer mire is determined by the patient's fixation, so the investigator must also assume the central corneal light reflex is near the center of the graft. Most idealized schematic drawings of the postkeratoplasty patient also place the pupil concentric to the graft (Fig. 1).

When this idealized relationship of graft, pupil, and central light reflex does not occur (Fig. 2), problems arise. Derivation of shape information from either a keratometer or from a topography system based on analysis of keratoscope images must be viewed with caution when the graft is decentered relative to the central corneal light reflex.[3] The practice of

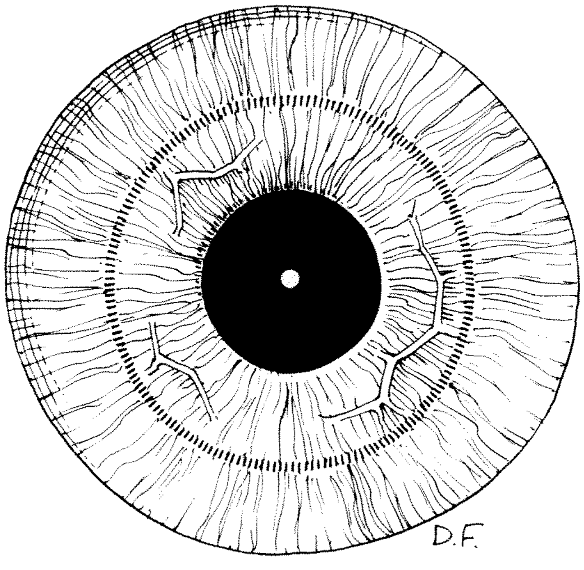

Fig. 1 (Millin and Maguire). Schema shows the idealized relationship of corneal graft, central corneal light reflex, and pupil after penetrating keratoplasty. The light reflex is centered on both the pupil and the graft.

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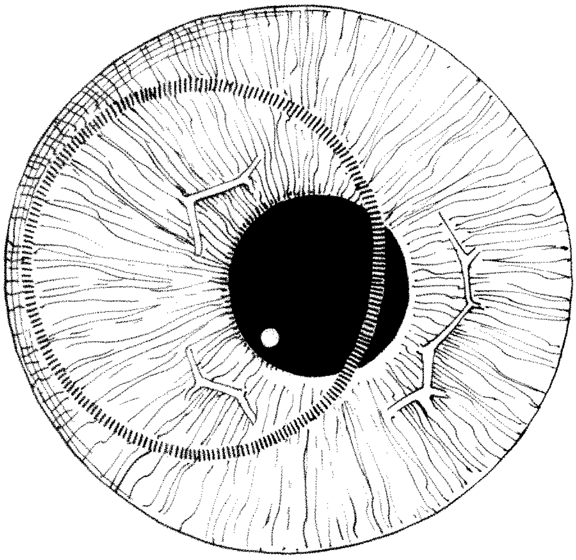

Fig. 2 (Millin and Maguire). Schema shows the corneal light reflex eccentric to the pupil in a patient with a decentered graft.

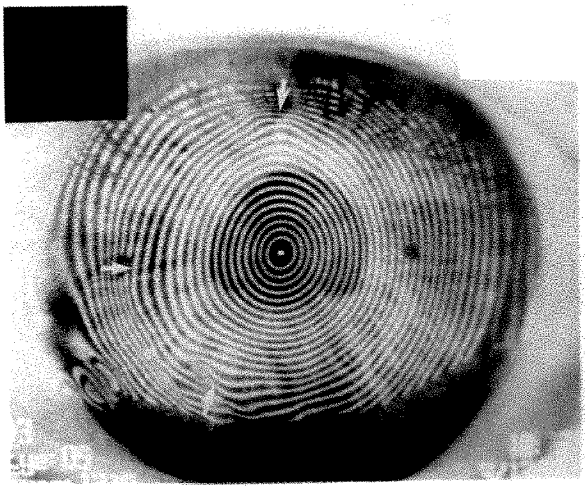

Fig. 3 (Millin and Maguire). Keratoscope image used as standard for a graft that is well centered relative to the corneal light reflex (vertex normal) (grade 1). The graft margins can be discerned by the irregularity in the keratoscope mires in the graft periphery (arrows).

locating semimeridians relative to the center of the graft is suspect because the measurement system (keratometer or keratoscope-based topography system) is not centered there.[4] A pupil decentered relative to the corneal light reflex or relative to the center of the graft could lead to corneal irregularity over the entrance pupil after relaxing incisions. Visually significant glare could result.[5]

This study asks whether topographic assumptions made in earlier studies of relaxing incisions are reasonable and whether topography analysis systems can be used to develop entry criteria for prospective studies.

Methods

We arbitrarily defined four criteria for entry into a study of severe postkeratoplasty astigmatism. Two of the criteria relate to the relative position of the graft, the pupil, and the central corneal light reflex (vertex normal): (1) graft well centered relative to the corneal light reflex, and (2) corneal light reflex within 0.5 mm of the center of the entrance pupil. The grading method for these requirements is based on examination of videokeratoscope images obtained with the Corneal Modeling System (Computed Anatomy, New York, New York).[6] Graft decentration is rated on a scale of 1 to 4, on the basis of comparison with standard videokeratographs (Figs. 3 through 6). A score of 1 or 2 was considered good centration and a score of 3 or 4 was considered unacceptable decentration. Three independent observers rated graft centration relative to the vertex normal. The graft was given the score agreed on by at least two of the observers. We used a qualitative measure because the topography system could not accurately identify scar at the graft-host interface.

The distance between the center of the entrance pupil and the corneal light reflex was determined by transposing a series of concentric circles over the pupil on the videokeratograph image and marking the center of the pupil on the video screen. The cursor on the topography system measured the distance between the central light reflex and the pupil center mark.

We developed one criterion to ensure that the topography system could analyze the graft near the central corneal light reflex in all semimeridians. This goal is achieved when the Corneal Modeling System can completely digitize the central ten rings of the videokeratograph image. This minimum requirement is necessary to obtain useful information about distribution of power on the graft surface.[7]

The final criterion concerns visual potential. An accurate refractive end point is difficult to obtain in patients with poor macular function. For that reason we required a preoperative,

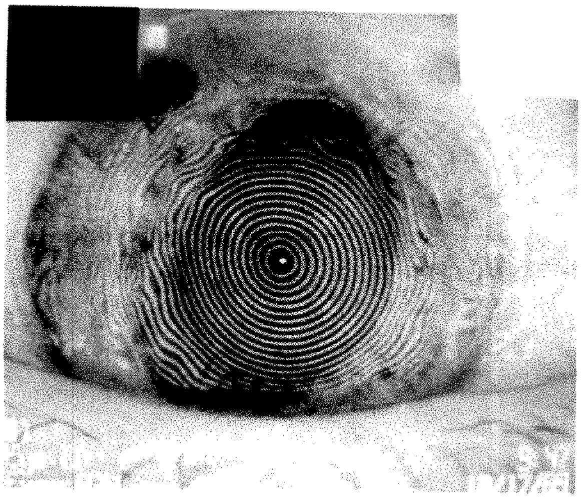

Fig. 4 (Millin and Maguire). Standard for grade 2 decentration. Vertex normal is slightly decentered relative to the graft.

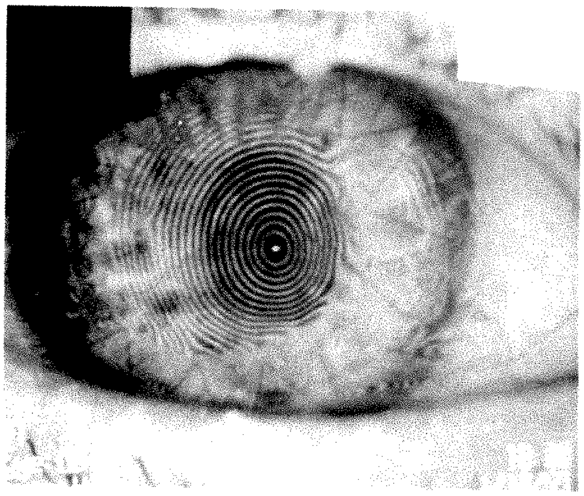

Fig. 5 (Millin and Maguire). Standard for grade 3 decentration. Vertex normal located well to the right and below the center of the graft.

spectacle- or pinhole-corrected visual acuity of greater than or equal to 20/40.

After establishing the entry criteria, we reviewed the records and videokeratograph images from the Corneal Modeling System of 20 eyes of 20 consecutive patients referred for the surgical correction of severe postkeratoplasty astigmatism between May 18, 1988, and April 18, 1990. We determined the percentage of eyes meeting all four criteria and the number of eyes meeting each individual requirement.

Results

Only seven eyes (35%) simultaneously met all four entry criteria (Table). Seventy percent met the visual acuity requirement. The distance between the corneal light reflex and the center of the entrance pupil was less than or equal to 0.5 mm from the center of the entrance pupil in 12 eyes (60%). A graft centration grade of 1 or 2 occurred in 18 eyes (90%). The Corneal Modeling System accurately digitized at least ten keratoscope rings in 18 eyes.

Discussion

This study shows how a topography analysis system can be used to develop entry criteria for studies of postkeratoplasty astigmatism. We studied factors that can cause improper location of relaxing incisions, induce glare, and compromise the accuracy of instruments that putatively measure corneal shape and refractive power. In the process, the study allows investigators interested in developing multicenter prospective trials to understand the heterogeneity of the patient population and the limitations of topography analysis.

The experience of the Prospective Evaluation of Astigmatic Keratotomy grant development group demonstrates the need for this type of information. Investigators from centers interested in the correction in severe postkeratoplasty astigmatism met on many occasions between

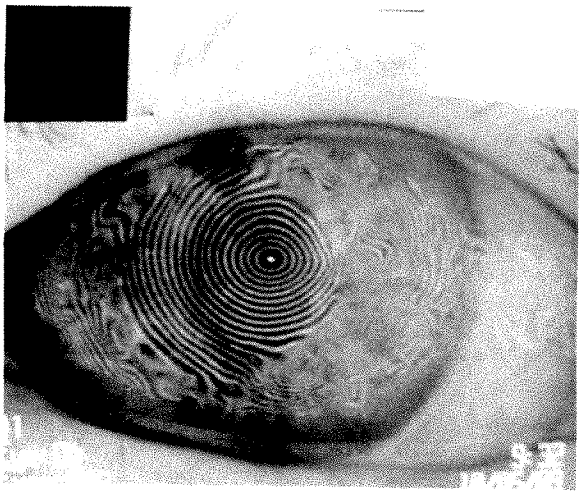

Fig. 6 (Millin and Maguire). Standard for grade 4 decentration. Vertex normal more displaced to the right.

TABLE
SUMMARY OF PATIENT DATA

PATIENT NO.*	BEST-CORRECTED VISUAL ACUITY OR PINHOLE VISUAL ACUITY	DISTANCE FROM VERTEX NORMAL TO PUPIL CENTER (MM)	GRAFT DECENTRATION RELATIVE TO VERTEX NORMAL	NO. OF KERATOSCOPE RINGS DIGITIZED
1	20/70	0.3	2	10
2	20/40	0.0	2	11
3	20/100	0.8	3	12
4	20/100	0.3	1	16
5	20/25	0.0	1	15
6	20/40	0.0	2	16
7	20/25	0.8	1	13
8	20/25	0.7	2	13
9	20/20	0.6	2	8
10	20/20	0.0	2	17
11	20/30	0.3	4	8
12	20/40	0.0	2	10
13	20/20	0.6	1	14
14	20/80	0.5	2	15
15	20/60	0.7	2	17
16	20/30	0.0	2	10
17	20/70	0.3	2	15
18	20/40	0.9	1	11
19	20/30	0.8	2	14
20	20/40	0.0	1	14

*Patients 2, 5, 6, 10, 12, 16, and 20 met all four entry criteria.

1986 and 1990 to develop the Prospective Evaluation of Astigmatic Keratotomy study. The group recently abandoned grant development in part because of lack of consensus concerning entry criteria and disagreement over the place of topography analysis systems in planning surgery and evaluating results. Our study provides some of the information needed to build group consensus.

The most encouraging finding of the study is that the vertex normal was located close to the center of the graft in 18 (90%) of the eyes studied. The algorithms that calculate corneal shape information from keratoscope images assume the vertex normal is located close to the apex of the cornea. The surgeon using topography information to alter graft shape needs a map that shows graft shape. When the vertex normal and the center of a corneal graft are misaligned, artifact is induced in the topography maps, artifact aggravated when severe astigmatism and irregularity are present on the graft.[3] Two (10%) of our patients showed this type of misalignment. It may be dangerous to use keratometry or topography map information to plan relaxing incisions in this small subset of patients. This factor may contribute to the predictability problems encountered in astigmatic keratotomy in the keratoplasty group. Not having an alternative to keratometry and topography analysis does not lessen the danger. What should be done when the vertex normal is far from the center of the graft? Since we are interested in corneal shape relative to the center of the graft for biomechanical reasons, it may be reasonable to have the examiner reorient such eyes so that the light reflex is centered near the middle of the graft. Such a map would likely give better shape information even though it would not accurately represent the optical performance of the graft. This thought is offered as a hypothesis worth testing.

It is encouraging that the topography system could digitize a minimum of ten keratoscope rings in 18 eyes (90%). This finding suggests a user should be able to evaluate a large enough area of the central graft to make reasonable judgments on graft shape and location of steep hemimeridians in most patients. Earlier topography studies suggest that such information is important in planning relaxing incisions from topographic map information since steep semimeridians may not be orthogonal and may show disparities in refractive power.[7,8] The Table shows 17 patients (85%) simultaneously had good graft centration relative to the vertex normal and a minimum of ten rings digitized.

Only 12 of our patients (60%) showed good alignment of the pupil and vertex normal. Eccentric location of the pupil relative to the center of the graft and the vertex normal causes concerns about the optical performance of the graft after a relaxing incision. If the pupil is located eccentrically relative to the vertex normal, and transverse keratotomies are centered relative to the vertex normal, significant optical distortion may occur over the area surrounding the entrance pupil.[5] Reduced optical performance and increased glare will result. Only 11 (55%) of our study group conformed to the idealized arrangement of pupil, light reflex, and graft shown in Figure 1 (Table).

Spectacle-corrected or pinhole visual acuity of at least 20/40 was included to ensure that retinal function was sufficient to allow a reasonable refractive end point. Refractive cylinder may be underestimated when retinal function is compromised. When this factor is added to the three above, only seven (35%) of our group meet entry requirements.

Our use of a qualitative test to evaluate graft decentration relative to the vertex normal can be criticized. We preferred to use a quantitative test, but the Computed Anatomy topography system does not show graft scarring well, and we were forced to use a measure that may be confusing to the topography neophyte. We are developing a new device that may allow us to measure this variable quantitatively.

Our results show that the idealized relationship of pupil, graft, and vertex normal (Fig. 1) does not apply to many patients in this population. Planners must deal with this topographic heterogeneity when they develop inclusion criteria and surgical plans for correcting astigmatism. They must understand the limitations as well as benefits of topography systems. Astigmatic keratotomy requires knowledge about the shape, optical performance, and biomechanics of the cornea. We cannot advance much farther by evaluating refractive error, Snellen acuity, and keratometry results alone. Topography analysis may not answer all our problems, but it does allow us to understand topographic heterogeneity in the keratoplasty population which in turn should allow improved study designs and hopefully improved results.

References

1. Lindstrom, R. L.: The surgical correction of astigmatism. A clinician's perspective. Refract. Corneal Surg. 6:441, 1990.
2. Swinger, C. A.: Postoperative astigmatism. Surv. Ophthalmol. 31:219, 1987.
3. Wang, J., Rice, D. A., and Klyce, S. D.: A new reconstruction algorithm for improvement of corneal topographical analysis. Refract. Corneal Surg. 5:379, 1989.
4. Waring, G. O. III: Making sense of keratospeak. II. Proposed conventional terminology for corneal topography. Refract. Corneal Surg. 5:362, 1989.
5. Uozato, H., and Guyton, D. L.: Centering corneal surgical procedures. Am. J. Ophthalmol. 103:264, 1987.
6. Gormley, D. J., Gersten, M., Koplin, R. S., and Lubkin, V.: Corneal modeling. Cornea 7:30, 1988.
7. Maguire, L. J., and Bourne, W. M.: Corneal topography of transverse keratotomies for astigmatism after penetrating keratoplasty. Am. J. Ophthalmol. 103:323, 1989.
8. Frangieh, G. T., Kwitko, S., and McDonnell, P. J.: Prospective corneal topographic analysis in surgery for postkeratoplasty astigmatism. Arch. Ophthalmol. 109:506, 1991.

OPHTHALMIC MINIATURE

'He has no eye,' I replied categorically. 'Just take a look at where his eye ought to be. Your baby has a strange sort of swelling.'

'Give him some drops, then,' said the woman fearfully.

'You're joking! What sort of drops? No drops are going to do him any good!'

'You wouldn't leave him without an eye, would you?'

'But he *has* no eye, I tell you.'

'He had one the day before yesterday!' the woman exclaimed in desperation. (God!)

Mikhail Bulgakov, *A Country Doctor's Notebook*
London, Collins Harvill, 1990, p. 108

Transscleral Nd:YAG Laser Cyclophotocoagulation With a Contact Lens

Ruthanne B. Simmons, M.D., M. Bruce Shields, M.D., Marino Blasini, M.D.,
Mark Wilkerson, M.D., and Robert A. Stern, Ph.D.

Transscleral Nd:YAG laser cyclophotocoagulation was performed on 100 consecutive patients. A contact lens designed specifically for this operation was used, and the results were compared to those of a previously reported series of 100 patients in which the same procedure was performed without the lens. The lens provided intraoperative advantages of eyelid separation, compression and blanching of the conjunctiva at the treatment site, and precise measurements for placement of the laser applications. Early postoperative advantages were reduced conjunctival burns and less hyperemia. However, the long-term results were comparable between the two series, with the exception of a higher incidence of phthisis when the lens was used. The thinning and blanching of the conjunctiva may increase the percentage of laser energy reaching the ciliary processes, which suggests a need for reduced energy levels when using the lens.

THE CONCEPT OF transscleral laser cyclophotocoagulation was introduced by Vucicevic and associates[1] in 1969 and pioneered by Beckman and colleagues[2] in the early 1970s. A ruby laser was initially used, but Beckman and Sugar[3] subsequently observed that a neodymium laser provided a more useful wavelength for penetrating sclera and enhancing energy absorption at the level of the ciliary epithelium. With the commercial availability of Nd:YAG lasers, transscleral Nd:YAG laser cyclophotocoagulation has become an increasingly popular cyclodestructive procedure.[4-8]

Several techniques have been used in performing transscleral Nd:YAG laser cyclophotocoagulation. The laser energy may be delivered by either a slit lamp or fiberoptic contact probe, and the laser mode may be either pulsed or continuous-wave. One of the most extensively studied techniques utilizes the slit-lamp delivery of laser energy in a pulsed, thermal mode.[4-7] Originally this procedure involved laser application through air without a lens interface. To facilitate the operation, we developed a contact lens that maintains eyelid separation, compresses and blanches the conjunctiva, and provides measurements for accurate laser placement.[9]

A study of the contact lens in human autopsy eyes disclosed similar histologic results[10] to those previously observed for transscleral Nd:YAG laser cyclophotocoagulation without a contact lens.[11] This study contains the results of a prospective clinical evaluation of transscleral Nd:YAG laser cyclophotocoagulation with the contact lens. We compared these findings to a previously reported series of 100 patients, in which the same protocol was used with no contact lens.[6]

Patients and Methods

All patients were entered prospectively and consecutively from the Glaucoma Service of the Duke University Eye Center. The patients selected for transscleral Nd:YAG laser cyclophotocoagulation were those at high risk of failure with standard glaucoma filtering surgery, including failed filtering operations, glaucoma in aphakia or pseudophakia, neovascular glaucoma, glaucoma associated with inflammation, and glaucoma after penetrating keratoplasty. All patients had an intraocular pressure that was thought to be inadequately controlled despite maximally tolerated medical therapy and

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All laser procedures in the study were performed by one of us (M.B.S., M.B., M.W.). Retrobulbar anesthetics containing a 50:50 mixture of 4% lidocaine and 0.75% bupivacaine with 150 USP U of hyaluronidase were given in all cases. With the patient positioned at the slit lamp, the eyelids were separated, and the contact lens was applied to the cornea and sclera with a viscous bridge of methylcellulose. If a prominent brow forced the lens inferiorly, preventing adequate vertical alignment, the lens was rotated so that the section removed from the peripheral holding portion was in the superior quadrant. The innermost of three etch marks was then aligned with the corneoscleral limbus at the 12 o'clock position. The other two marks, located 1 and 2 mm peripheral to this reference point, were used for placement of the laser applications. Three additional sets of marks, placed at the 3, 6, and 9 o'clock positions, aided in placement in all quadrants. Pressure was then applied to the eye with the contact lens in the area of treatment to compress and blanch the conjunctiva (Fig. 1).

The Nd:YAG laser was used in the free-running, thermal mode with a duration of 20 msec. The offset between the therapeutic and aiming beams was set at the maximum of 9, which corresponds to 3.6 mm in air. An average energy level of 7.6 J was used, with a mean of 32 evenly spaced applications for 360 degrees. Burns were placed 1.5 mm posterior to the surgical corneoscleral limbus superiorly and inferiorly and 1.0 mm nasally and temporally.

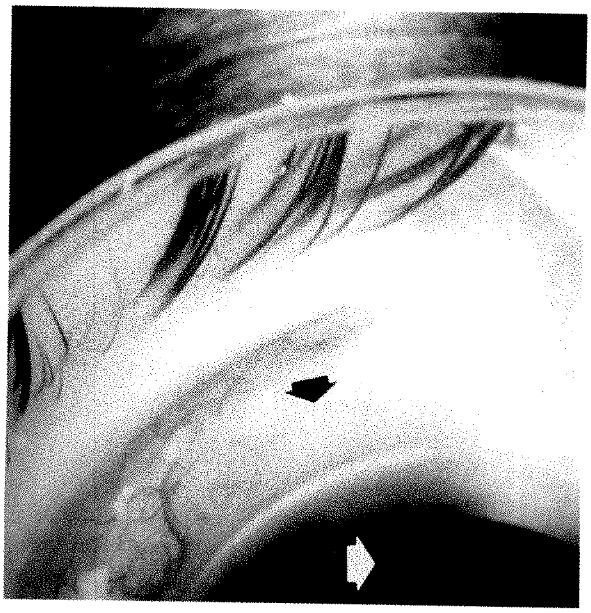

Fig. 1 (Simmons and associates). Slit-lamp view of the contact lens in position. The upper eyelid and lashes rest against the edge of the lens. Note the blanching of the conjunctival vessels (black arrow) adjacent to an area of unblanched vessels, and the central corneal protector (white arrow).

Dexamethasone, 12 mg, was injected subconjunctivally immediately after the procedure. The patients were given atropine 1% twice daily and an antibiotic/corticosteroid combination four times daily for ten days, or longer as required by the degree of inflammatory response. Miotic therapy was discontinued, but all other preoperative glaucoma medications were continued. Measurement of intraocular pressure and slit-lamp examination were performed two hours after the procedure.

Subsequent examinations at one day, two to four weeks, and every two to four months thereafter included measurement of visual acuity and intraocular pressure, slit-lamp examination and fundus examination, and recording a history of discomfort or other complaints. A decrease in vision was defined as a decrease of more than two lines of Snellen acuity or one low-vision category. Glaucoma medications were coded numerically, on the basis of a point value scale described previously.[12] A change of two or more in this scaled medication number in either direction was considered remarkable and recorded as an increase or decrease in medical therapy. A change in intraocular pressure of 2 mm Hg or more in either direction was considered remarkable. A change of less than 2 mm Hg was recorded as no change. Phthisis was defined as an intraocular pressure of zero with shrinkage of the globe. When the intraocular pressure reduction was inadequate one month or more after the treatment, one or more repeat procedures was performed, using the same basic protocol.

Only one eye per patient was included in the analysis of data. When both eyes of a patient were treated, one was randomly selected for analysis. In assessing the relationship between potential risk factors and intraocular pressure outcome, categoric data were analyzed by chi square and continuous data were analyzed by univariate analysis of variance.

Results

One hundred consecutive patients were included in the study. There were 55 women and

Transscleral Nd:YAG Laser Cyclophotocoagulation With a Contact Lens

Ruthanne B. Simmons, M.D., M. Bruce Shields, M.D., Marino Blasini, M.D.,
Mark Wilkerson, M.D., and Robert A. Stern, Ph.D.

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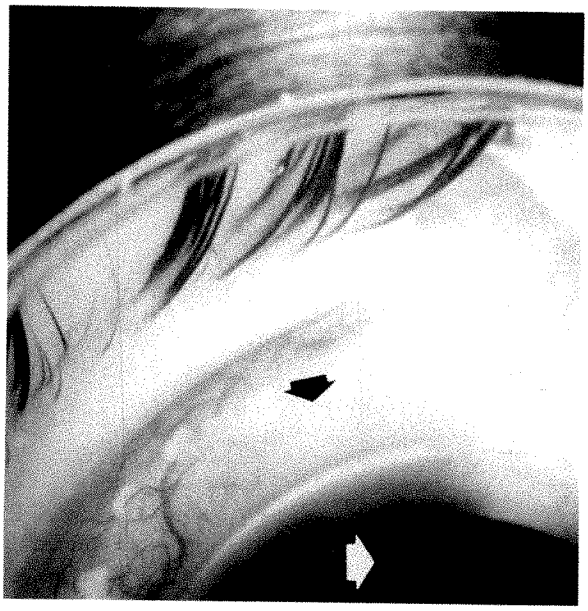

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One hundred consecutive patients were included in the study. There were 55 women and

TABLE 1

DIAGNOSTIC GROUPS

GLAUCOMA DIAGNOSIS	PATIENTS (N = 100)
Neovascular glaucoma	17
Glaucoma in aphakia	27
Glaucoma in pseudophakia	33
Glaucoma after penetrating keratoplasty	10*
Other	13†

*Four aphakic; five pseudophakic; one phakic.

†Three congenital glaucoma; three traumatic glaucoma; two primary open-angle glaucoma; two angle-closure glaucoma; one juvenile glaucoma; one pigmentary glaucoma; one glaucoma in aniridia.

TABLE 2

INTRAOCULAR PRESSURE CHANGE AT TWO AND 24 HOURS

INTRAOCULAR PRESSURE	PATIENTS NO. (%)	MEAN CHANGE (RANGE, MM HG)	MEAN % CHANGE
2 hrs (N = 98)*			
Decrease/same	81 (83)	−10.2 (+1 to −39)	−25.5 (+6 to −94)
Increase	17 (17)	+8.2 (+2 to +28)	+33.4 (+10 to +109)
24 hrs (N = 80)*			
Decrease/same	68 (85)	−16.5 (+1 to −41)	−41.9 (+6 to −82)
Increase	12 (15)	+6.0 (+2 to +14)	+29.1 (+6 to +67)

*N = patients with available data.

45 men with a mean age of 62.0 years (range, 22 to 90 years). Eighty-one subjects were white and 19 were black. Fifteen patients were phakic, 41 were aphakic, and 44 were pseudophakic. The most common diagnostic categories were glaucoma in aphakia, glaucoma in pseudophakia, and neovascular glaucoma (Table 1).

Seventy patients had previous intraocular glaucoma surgery, including argon laser trabeculoplasty in 18, a single filtering operation in 23, two or more filtering operations in eight, cyclocryotherapy in 14, transpupillary argon cyclophotocoagulation in two, previous transscleral Nd:YAG laser cyclophotocoagulation without the contact lens in two, and peripheral iridectomies in three patients.

The median pretreatment visual acuity was 20/400. Fifty-two patients had visual acuities better than or equal to 20/400 (median, 20/70), whereas the remaining 48 patients had visual acuities worse than 20/400 (median, hand motion). Two patients had no light perception. The mean pretreatment intraocular pressure was 34.6 mm Hg (range, 12 to 78 mm Hg). Ten patients with pretreatment intraocular pressures less than 20 mm Hg were treated because of either medication intolerance or diurnal pressure spikes of 21 to 28 mm Hg with documented progressive visual loss. The mean value of pretreatment medical therapy for the entire sample, on the basis of the medication point value scale described previously, was 9.2 (range, 0 to 21). Patients were followed up from four to 24 months (mean, 11 months).

At two and 24 hours after transscleral Nd:YAG laser cyclophotocoagulation, 81 (83%) and 68 (85%) patients, respectively, had no change or a decrease in intraocular pressure (Table 2). Of those patients who had an increase in intraocular pressure, the average increase was 8.2 mm Hg at two hours and 6.0 mm Hg at 24 hours.

At the two-month examination, 78 of 91 patients (86%) had a decreased intraocular pressure of greater than 2 mm Hg. Five of 91 patients (5%) had no change in intraocular pressure of more than 2 mm Hg, and eight of 91 (9%) had an increase in intraocular pressure. The mean intraocular pressure change for these groups is shown in Table 3.

At the final visit after the initial treatment, 56 patients had intraocular pressures between 7 and 20 mm Hg and required no further treatment. Eleven patients had a pressure less than 7 mm Hg, and ten were above 20 mm Hg, but no further treatment was thought to be indicated for these patients. In the remaining 23 patients, the final intraocular pressure after the initial treatment was thought to be inadequate (Table 4).

Twenty patients underwent repeat transscleral Nd:YAG laser cyclophotocoagulation treatments at our institution. An additional three patients underwent repeat transscleral Nd:YAG laser cyclophotocoagulation elsewhere, but the data on their repeat procedures are not included in this study.

After the first repeat treatment at our institution, ten patients had final intraocular pressures between 7 and 20 mm Hg and required no further surgical treatment. One patient developed phthisis, and two had final intraocular pressures of 22 mm Hg, but no further laser

TABLE 3
INTRAOCULAR PRESSURE CHANGE AT TWO MONTHS

INTRAOCULAR PRESSURE	PATIENTS NO. (%) (N = 91)*	MEAN CHANGE (RANGE, MM HG)	MEAN % CHANGE
Decrease/same	83 (91)	−19.9 (+1 to −54)	−54.7 (+4 to −100)
Increase	8 (9)	+11.0 (+3 to +37)	+45.9 (+9 to +115)

*N = patients with available data.

TABLE 4
FINAL INTRAOCULAR PRESSURE AFTER FIRST TREATMENT

INTRAOCULAR PRESSURE	PATIENTS (N = 100)
7-20 mm Hg	56
< 7 mm Hg	11
> 20 mm Hg, no repeat treatment	10
> 20 mm Hg, with repeat treatment	23

treatment was recommended. Seven patients had additional repeat transscleral Nd:YAG laser cyclophotocoagulation; four required two repeats, two had three repeats, and one patient had four repeats.

After one or more treatments, 69 patients had final intraocular pressures between 7 and 20 mm Hg (Table 5). Eighty-four patients had a decrease in their intraocular pressure, ranging from −2 to −45 mm Hg with a mean of −20.8 mm Hg, which represents a mean percentage decrease of 53.8%. Five patients did not have a pressure change of more than 2 mm Hg, five had an increase of more than 2 mm Hg, and six patients developed phthisis.

None of the six patients who developed phthisis had had previous cyclodestructive surgery. One patient with neovascular glaucoma had two transscleral Nd:YAG laser cyclophotocoagulation treatments because his intraocular pressure was 56 mm Hg one month after initial treatment. The other five patients underwent only a single treatment. Two patients had undergone previous trabeculectomies, and one patient had undergone cyclodialysis. Three patients had neovascular glaucoma: one had had no previous surgery, and two had had vitrectomies with membrane peeling and fluid-gas exchange. Three patients were phakic, two were aphakic, and one was pseudophakic.

At the final visit, five patients required an increase in their glaucoma medications as compared to their pretreatment medications, and 62 required fewer medications.

Fifty-one patients had no change in visual acuity. Twelve had an improvement, and 35 patients had a decrease. The visual acuity in six patients decreased to no light perception. Of these six individuals, the preoperative visual acuity was counting fingers in two, hand motions in three, and light perception in one. Five of these six patients had neovascular glaucoma.

Of the 52 patients with pretreatment visual acuities greater than or equal to 20/400, 22 lost two or more Snellen lines of visual acuity by the final visit (nine lost two lines, seven lost three to four lines, three lost five to six lines, and three patients lost seven to nine lines). Of the 48 patients with pretreatment visual acuity worse than 20/400, ten patients had an improvement (five improved to better than 20/400, with 20/25 and 20/60 in two patients), 20 had no change, and 17 patients had a decrease in their visual acuity.

The following variables were significantly associated with the final intraocular pressure result: (1) pretreatment visual acuity (27 of 48 [56%] of patients with a pretreatment visual acuity worse than 20/400 had final pressures of 7 to 20 mm Hg, compared to 42 of 52 [81%] of those with a visual acuity better than or equal to 20/400; $P = .025$); (2) race (60 of 81 [74%] of white patients had final intraocular pressures of 7 to 20 mm Hg, compared to nine of 19 [47%] of the black patients; $P = .019$); and (3) type of glaucoma (patients with neovascular glaucoma had the lowest success, whereas patients with glaucoma in pseudophakia had the best intraocular pressure outcome [Table 6]). There was also a significant correlation between the final intraocular pressure and the intraocular pressure at two months ($r = .46$, $P = .001$).

Factors that were analyzed and found not to be significantly associated with the final intraocular pressure included age, pretreatment intraocular pressure, gender, the amount of laser energy delivered, and the number of spots delivered.

Postoperative complications included white conjunctival burns at the sites of the laser applications, which usually were not detectable by the first postoperative day, and conjunctival hyperemia, which was typically mild and cleared within the first one to two weeks. Anterior uveitis was also seen in all patients, although this was judged to be mild in approxi-

TABLE 5
FINAL INTRAOCULAR PRESSURE AFTER ONE OR MORE TREATMENTS

INTRAOCULAR PRESSURE	PATIENTS (N = 100)	MEAN PRESSURE (MM HG)	MEAN CHANGE (MM HG)	MEAN % CHANGE
7-20 mm Hg	69	14.5	−18.5	−49.3
< 7 mm Hg	13	2.2	−36.6	−92.9
> 20 mm Hg	18	26.3	−11.8	−19.8

mately one half of the patients, moderate in 20%, and severe in 30%. Most patients retained a chronic, low-grade flare. Only two patients complained of severe pain. Other complications included four hyphemas, four vitreous hemorrhages, one vitreitis, four posttreatment choroidal detachments, one acute cystoid macular edema, and one patient with possible malignant glaucoma.

Discussion

In vitro studies with human autopsy eyes disclosed no histologic differences when transscleral Nd:YAG laser cyclophotocoagulation was performed with[10] and without[11] the contact lens used in this study. This was not surprising, since two of the main advantages of the contact lens are believed to be compression and blanching of the conjunctiva, neither of which would be a factor in the autopsy eyes. In the living eye, however, these two factors might enhance the percentage of laser energy reaching the ciliary body and influence the surgical outcome. The purpose of this study, therefore, was to compare the results of a clinical trial in which the contact lens was used to the results of a previously reported trial in which 100 patients were treated with the same transscleral Nd:YAG laser cyclophotocoagulation protocol, except for the absence of a contact lens.[6]

The patient populations in the two studies were comparable. In the previous study with no contact lens, the baseline mean intraocular pressure was 38 mm Hg with a range of 18 to 80 mm Hg; the baseline visual acuity was equal to or better than 20/400 in 53 of the 100 patients; and the most common glaucoma types were neovascular glaucoma in 27, glaucoma in aphakia in 27, and glaucoma in pseudophakia in 31 patients. Twenty-five patients in the previous study, as opposed to 18 patients in this study, had undergone previous cyclodestructive surgery.

TABLE 6
RELATIONSHIP BETWEEN GLAUCOMA TYPE AND FINAL INTRAOCULAR PRESSURE

GLAUCOMA DIAGNOSTIC GROUP	INTRAOCULAR PRESSURE OUTCOME		
	7-20 MM HG NO. (%)	< 7 MM HG NO. (%)	> 20 MM HG NO. (%)
Neovascular	10 (59)	4 (24)	3 (18)
In aphakia	19 (70)	3 (11)	5 (19)
In pseudophakia	25 (76)	3 (9)	5 (15)
After penetrating keratoplasty	7 (70)	2 (20)	1 (10)
Other	8 (62)	1 (8)	4 (31)

The postoperative results were also similar in the two groups treated with and without the contact lens. Two hours after the initial treatment, there was either no change or a decrease in intraocular pressure in 81 of 98 (83%) and 68 of 87 (79%) of the patients, respectively, whereas 68 of 80 (85%) and 78 of 86 (91%), respectively, had either the same or a decreased pressure from baseline on the first postoperative day. After the initial treatment, 56 of 100 (56%) and 51 of 100 (51%) patients, respectively, had a final intraocular pressure between 7 and 20 mm Hg. Those for whom further surgical reduction of the intraocular pressure was thought to be indicated after the initial treatment were 23 of 100 (23%) and 32 of 100 (32%) patients, respectively. When the results of all treatments were included, a final intraocular pressure between 7 and 20 mm Hg was seen in 69% and 65%, respectively. However, there were six cases of phthisis among the 100 patients in whom the lens was used, compared to none when it was not used.

Factors associated with the final intraocular pressure result differed somewhat between the two groups. In both study populations, neovascular glaucoma was associated with the poorest result, whereas patients with glaucoma in pseudophakia had the best intraocular pressure response. However, a higher mean age and a lower baseline intraocular pressure correlated with a better pressure result in the group without the contact lens, but not in those patients in whom the lens was used. Conversely, those in whom the lens was used had a better final intraocular pressure result in association with a better baseline visual acuity, white race, and a favorable intraocular pressure at two months after treatment.

Visual acuity results were similar between the two groups. The final visual acuity was unchanged or improved, as compared to the baseline level, in 63 of 100 (63%) of those treated with the lens and 50 of 100 (50%) of the group in which it was not used. The extent of visual reduction among those who lost visual acuity was comparable between the two groups.

Postoperative complications were also similar between the two groups with one notable exception. By compressing and blanching the conjunctiva, the contact lens markedly reduced the degree of conjunctival burn, as compared to the same amount of laser treatment without the lens (Fig. 2). The reduction in conjunctival burns resulted in a more rapid resolution of the conjunctival hyperemia when the lens was used.

Both groups had relatively low rates of other postoperative complications, especially as compared to those reported with cyclocryotherapy.[13] In addition to the low incidence of transient postoperative intraocular pressure increase, which is a significant complication of cyclocryotherapy, transscleral Nd:YAG laser cyclophotocoagulation, with or without the use of the contact lens, was associated with a much lower incidence of severe pain and inflammation, as compared to that with cyclocryotherapy.

Schuman and colleagues,[8] using a fiberoptic contact probe delivery of continuous-wave Nd:YAG laser, reported intraocular pressure results comparable to those in this study, with a lower rate of visual acuity reduction. Furthermore, lower energy levels were required with the contact probe, which may be explained by a combination of conjunctival compression and reduced light scatter.

Fankhauser, Rol, and Kwasniewska[14] stated that using a contact lens with the slit-lamp-delivery of transscleral Nd:YAG laser cyclophotocoagulation eliminates most of the differences in results between the slit-lamp and contact probe techniques of laser delivery. When slit-lamp delivery transscleral Nd:YAG laser cyclophotocoagulation is performed without the contact lens, between 20% and 50% or more of the light may be reflected from the sclera by surface scatter and bulk scatter.[14] Backscattered rays within the sclera may also cause heating of the sclera. However, when a contact lens is used, reflected light can be reduced to less than 1%, and backscatter within the sclera can be decreased, allowing energy to exit through the contact lens.[14,15] Compression and blanching of

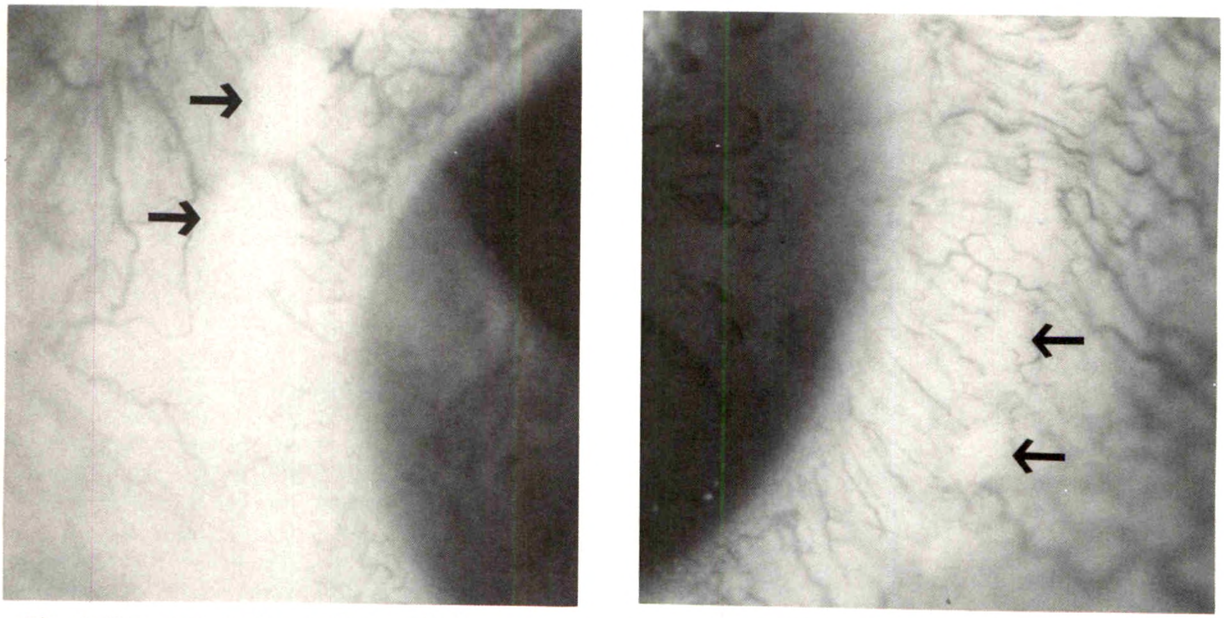

Fig. 2 (Simmons and associates). Slit-lamp view of an eye immediately after transscleral Nd:YAG laser cyclophotocoagulation in which 180 degrees was treated without the use of the contact lens (left) and 180 degrees with the use of the contact lens (right). The black arrows indicate areas of conjunctival burning that are decreased when the contact lens is used. (All eyes in the present study were treated for 360 degrees with the lens.)

the conjunctiva, along with reduced light scatter, may increase the amount of laser energy reaching the ciliary body and decrease heating within the sclera when the contact lens is used. This possibility is supported by the results of Schuman and colleagues[8] and Fankhauser, Rol, and Kwasniewska,[14,15] as well as the increased phthisis rate found in this study when the contact lens is used.

The higher rate of phthisis found when the contact lens is used cannot be explained on the basis of previous cyclodestructive surgery. None of the patients in whom phthisis developed had had cyclodestructive surgery. It is possible that the study done with the contact lens more accurately reflects the expected outcome of cyclodestructive surgery in these patients with advanced glaucoma. Alternatively, the contact lens may actually increase the amount of energy being delivered to the ciliary body, although this cannot be proved in our study.

This study supports the value of a contact lens for the slit-lamp delivery of transscleral Nd:YAG laser cyclophotocoagulation. The only late postoperative difference, as compared to the same operation without a contact lens, was a higher incidence of phthisis when using the lens. On the basis of these observations, we are now evaluating lower energy levels to find the optimum parameters for transscleral Nd:YAG laser cyclophotocoagulation with a contact lens.

References

1. Vucicevic, Z. M., Tsou, K. C., Nazarian, I. H., Scheie, H. G., and Burns, W. P.: A cytochemical approach to the laser coagulation of the ciliary body. Bibl. Ophthalmol. 79:467, 1969.
2. Beckman, H., Kinoshita, A., Rota, A. N., and Sugar, H. S.: Transscleral ruby laser irradiation of the ciliary body in the treatment of intractable glaucoma. Trans. Am. Acad. Ophthalmol. Otolaryngol. 76:OP423, 1972.
3. Beckman, H., and Sugar, H. S.: Neodymium laser cyclocoagulation. Arch. Ophthalmol. 90:27, 1973.
4. Devenyi, R. G., Trope, G. E., Hunter, W. H., and Badeeb, O.: Neodymium:YAG transscleral cyclocoagulation in human eyes. Ophthalmology 94:1519, 1987.
5. Klapper, R. M., Wandel, T., Donnenfeld, E., and Perry, H. D.: Transscleral neodymium:YAG thermal cyclophotocoagulation in refractory glaucoma. A preliminary report. Ophthalmology 95:719, 1988.
6. Hampton, C., Shields, M. B., Miller, K. N., and Blasini, M.: Evaluation of a protocol for transscleral neodymium:YAG cyclophotocoagulation in one hundred patients. Ophthalmology 97:910, 1990.
7. Trope, G. E., and Ma, S.: Mid-term effects of neodymium:YAG transscleral cyclophotocoagulation in glaucoma. Ophthalmology 97:73, 1990.
8. Schuman, J. S., Puliafito, C. A., Allingham, R. R., Belcher, C. D., Bellows, A. R., Latina, M. A., and Shingleton, B. J.: Contact transscleral continuous wave neodymium:YAG laser cyclophotocoagulation. Ophthalmology 97:571, 1990.
9. Shields, M. B., Blasini, M., Simmons, R. B., and Erickson, P. J.: A contact lens for transscleral Nd:YAG cyclophotocoagulation. Am. J. Ophthalmol. 108:457, 1989.
10. Simmons, R. B., Blasini, M., Shields, M. B., and Erickson, P. J.: Comparison of transscleral Nd:YAG cyclophotocoagulation with and without a contact lens in human autopsy eyes. Am. J. Ophthalmol. 109:174, 1990.
11. Hampton, C., and Shields, M. B.: Transscleral neodymium-YAG cyclophotocoagulation. A histologic study of human autopsy eyes. Arch. Ophthalmol. 106:1121, 1988.
12. Farrar, S. M., Shields, M. B., Miller, K. N., and Stoup, C. M.: Risk factors for the development and severity of glaucoma in the pigment dispersion syndrome. Am. J. Ophthalmol. 108:223, 1989.
13. Brindley, G., and Shields, M. B.: Value and limitations of cyclocryotherapy. Graefes Arch. Clin. Exp. Ophthalmol. 224:545, 1986.
14. Fankhauser, F., Rol, P., and Kwasniewska, S.: Considerations and methods for laser surgery in the anterior and posterior segments. Int. Ophthalmol. Clin. 30:130, 1990.
15. ———: Optical aids and their application. Int. Ophthalmol. Clin. 30:123, 1990.

Influence of Betaxolol and Timolol on the Visual Fields of Patients With Glaucoma

Christian Messmer, M.D., Josef Flammer, M.D., and Daniela Stümpfig

In a double-masked study, 40 patients with primary open-angle glaucoma were randomly assigned to treatment with betaxolol 0.5% or timolol 0.5% in both eyes twice daily. Visual fields and intraocular pressures were studied. Perimetry was performed with the Octopus G1 program two weeks after a washout period and three, six, 12, and 18 months after initiation of treatment. Both drugs reduced intraocular pressure. The reduction in intraocular pressure in the timolol-treated group was more pronounced than that in the betaxolol-treated group; the difference, however, was not statistically significant. In both treatment groups, the visual fields tended to improve during the first six months of treatment and remained stable or tended to deteriorate thereafter. The treatment effect on the visual field was better in the betaxolol-treated group than it was in the timolol-treated group ($P = .041$).

INCREASED INTRAOCULAR PRESSURE is considered the main pathogenetic factor for glaucomatous optic atrophy, and control of intraocular pressure is believed to influence the progression of such atrophy favorably. However, the evidence for this hypothesis consists mainly of clinical impressions. The influence of glaucoma treatment on visual function has not been well studied.[1-6]

Topically applied beta-blockers reduce intraocular pressure efficiently without marked subjective side effects and are therefore the drug of choice for most patients with glaucoma. Timolol was introduced for glaucoma treatment more than a decade ago.[7] However, clinical observations as well as controlled studies showed that topically applied beta-blockers can cause systemic side effects.[8,9] The contraindications for systemic treatment, therefore, had to be adopted for local treatment also. One of the main problems is bronchoconstriction in susceptible patients.[10-12] The incidence of patients who have asthma and chronic obstructive lung disease and glaucoma is substantial. In the early 1980s, betaxolol, a cardioselective beta-blocking agent, was introduced.[13,14] Although betaxolol may provoke asthma,[15] it seems to be more well tolerated than nonspecific beta-blockers.

Betaxolol may have fewer systemic side effects than timolol, which is also a reference drug used in the treatment of glaucoma, but betaxolol may not reduce intraocular pressure as well as timolol.[16,17] Therefore, betaxolol's influence on visual field survival may not be as beneficial as that of timolol. We investigated the influence of betaxolol and timolol on visual fields of patients with glaucoma in a double-masked, 18-month study.

Subjects and Methods

Patients were included in this study if they had the following: (1) intraocular pressure equal to or greater than 24 mm Hg, (2) an early glaucomatous visual field defect, and (3) clinical evidence of glaucomatous optic-nerve head damage.

Patients with systemic disease, such as diabetes mellitus, and patients with contraindications to beta-blocker treatment were excluded. None of the patients was being treated with any other local or systemic regimen. All patients were from the outpatient glaucoma service of the University of Basel Eye Clinic and gave their

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cannot be extended to apply to other types of populations, such as patients with advanced defects or normal-tension glaucoma. Nonetheless, a topically applied beta-blocker, especially betaxolol, is an effective treatment for patients who have early stages of glaucomatous visual field defects.

References

1. Sponsel, W. E., Dallas, N. L., and Burbridge, L.: Visual field survival. The response to timolol therapy in open-angle glaucoma. Br. J. Ophthalmol. 67:220, 1983.
2. Demmler, N., and Müller-Bardoff, G.: Zunahme von Gesichtsfelddefekten unter Timolol-Langzeitbehandlung bei Patienten mit Weitwinkelglaukom-Beobachtungen in der augenärztlichen Praxis. Klin. Monatsbl. Augenheilkd. 183:53, 1983.
3. Sponsel, W. E.: Quantification and monitoring of visual field defects and a prospective, randomized comparison of pilocarpine and timolol using computerized perimetry. Surv. Ophthalmol. 33(suppl.):427, 1989.
4. Crick, R. P., Vogel, R., Newson, R. B., Shipley, M. J., Blackmore, H., Palmer, A., and Bulpitt, C. J.: The progress of the visual field in chronic simple glaucoma and ocular hypertension treated topically with pilocarpine or with timolol. Eye 4:563, 1990.
5. Epstein, D. L., Krug, J. H., Hertzmark, E., Remis, L. L., and Edelstein, D. J.: A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. Ophthalmology 96:1460, 1989.
6. Flammer, J., Robert, Y., and Gloor, B.: Influence of pindolol and timolol treatment on the visual fields of glaucoma patients. J. Ocular Pharmacol. 2:305, 1986.
7. Zimmerman, T. J.: Timolol update. Surv. Ophthalmol. 28(suppl.):227, 1983.
8. Flammer, J., and Barth, D.: Kardiovaskuläre Effekte bei lokal appliziertem Timolol. Klin. Monatsbl. Augenheilkd. 176:561, 1980.
9. Fraunfelder, F. T.: Ocular beta-blockers and systemic effects. Arch. Intern. Med. 146:1073, 1986.
10. Weinreb, R. N., van Buskirk, E. M., Cherniack, R., and Drake, M.: Long-term betaxolol therapy in glaucoma patients with pulmonary disease. Am. J. Ophthalmol. 106:162, 1988.
11. Schoene, R. B., Abuan, T., Ward, R. L., and Beasley, C. H.: Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis. Am. J. Ophthalmol. 97:86, 1984.
12. Van Buskirk, E. M., Weinreb, R. N., Berry, D. P., Lustgarten, J. S., Podos, S. M., and Drake, M. M.: Betaxolol in patients with glaucoma and asthma. Am. J. Ophthalmol. 101:531, 1986.
13. Berrospi, A. R., and Leibowitz, H. W.: Betaxolol. A new beta-adrenergic blocking agent for the treatment of glaucoma. Arch. Ophthalmol. 100:913, 1982.
14. Giudicelli, J. F., Richer, C., Ganansia, J., Warrington, S., Abriol, C., and Rullière, R.: Betaxolol. Beta-adrenoceptor blocking effects and pharmacokinetics in man. In Morselli, P. L. (ed.): Laboratories d'Etudes et de Recherches Scientifiques-SYNTHELABO, vol. 1. New York, Raven Press, 1983, pp. 89–92.
15. Cervantes, R., Hernandez, H. H., and Frati, A.: Pulmonary and heart rate changes associated with nonselective beta-blocker glaucoma therapy. J. Toxicol. Cutan. Ocular Toxicol. 5:185, 1986.
16. Feghali, J. G., and Kaufman, P. L.: Decreased intraocular pressure in the hypertensive human eye with betaxolol, a beta$_1$-adrenergic antagonist. Am. J. Ophthalmol. 100:777, 1985.
17. Allen, R. C., Hertzmark, E., Walker, A. M., and Epstein, D. L.: A double-masked comparison of betaxolol vs timolol in the treatment of open-angle glaucoma. Am. J. Ophthalmol. 101:535, 1986.
18. Flammer, J., Jenni, A., Bebié, H., and Keller, B.: The Octopus glaucoma G1 program. Glaucoma 9:67, 1987.
19. Flammer, J., Drance, S. M., Augustiny, L., and Funkhouser, A.: Quantification of glaucomatous visual field defects with automated perimetry. Invest. Ophthalmol. Vis. Sci. 26:176, 1985.
20. Flammer, J., and Drance, S. M.: The effect of acetazolamide on the differential threshold. Arch. Ophthalmol. 101:1378, 1983.
21. Demailly, P., Aubrier, G., Abadie, P.: Timolol et pronostic fonctionnel périmétrique du glaucome primitif à angle ouvert. J. Fr. Ophtalmol. 8:383, 1985.

Ultrasonic Tissue Characterization of Uveal Melanoma and Prediction of Patient Survival After Enucleation and Brachytherapy

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Jonathan A. Coleman, Daniel Rosberger, M.D., Robert M. Ellsworth, M.D.,
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We performed survival studies on 136 patients with uveal malignant melanoma who were examined with ultrasonic tissue characterization before treatment with cobalt-60 brachytherapy (74 patients) or enucleation (62 patients). Mean follow-up time was 58.7 months for the brachytherapy group and 59.0 months for the enucleated group. The maximal follow-up time was nearly ten years. Univariate survival analysis showed that patients with small tumors (< 250 mm^3, 49 patients) had a higher five-year survival when treated with brachytherapy than when treated with enucleation. No patients in this study with tumor volumes greater than 1,500 mm^3 (13 patients) were treated with brachytherapy. For tumors of intermediate size (74 patients), survival analysis did not indicate appreciable differences between the treatment options. However, multivariate models including two ultrasonic tissue characterization variables, scatterer size and concentration, showed appreciable intergroup differences in the dependence of survival on these factors. Results suggest that tissue properties detectable with ultrasonic techniques are related to differences in patient survival and may be used for treatment planning for tumors of intermediate size.

The issue of rational treatment for uveal melanoma (whether to treat with radiotherapy and attempt to preserve vision or to enucleate) is analytically difficult. The difficulties include the rarity of the tumor (approximately 1,500 new cases per year in the United States) and the long duration of follow-up needed to draw statistical inferences about treatment options (mean patient survival duration is over five years). Clinical studies must also consider the influence of known covariate factors such as tumor size and location, patient characteristics, and cell morphometry, as well as the possibility of unknown forms of bias.

Retrospective clinical studies comparing survival rates of patients whose eyes were enucleated and patients treated with radiotherapy are equivocal or indicate no marked difference in long-term survival for patient cohorts as a whole.[1-6]

Histopathologic and micromorphometric studies of tissue from enucleated eyes have indicated that the underlying morphologic characteristics of tissue and mitotic state correlate with patient survival and may be used ex post facto to provide an estimate of survival.[7-12] These studies show that survival is influenced, in quantifiable terms, by the underlying morphologic characteristics of the tumor.

Previously, we demonstrated that uveal malignant melanoma can be differentiated into acoustic subgroups using ultrasonic tissue characterization techniques and that tissue characteristics correlate with morphometric

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TABLE
DEMOGRAPHIC DATA AND CLINICAL BACKGROUND OF PATIENTS TREATED WITH BETAXOLOL OR TIMOLOL

	BETAXOLOL-TREATED PATIENTS	TIMOLOL-TREATED PATIENTS
No. of patients	20	20
No. of patients who withdrew during baseline study	—	2
No. of patients who discontinued treatment because of side effects or adverse reactions	1	1
No. of patients who completed the study	19	17
No. of eyes that completed the study	38	34
Gender (M/F)	14/5	9/8
Age (yrs)	66.2 (S.D. ± 9.4)	66.8 (S.D. ± 9.8)
Intraocular pressure after washout period (mm Hg)	24.1 (S.D. ± 4.3)	24.4 (S.D. ± 3.7)
Mean defect after washout period (dB)		
R.E.	2.2 (S.D. ± 3.1)	3.4 (S.D. ± 2.2)
L.E.	2.8 (S.D. ± 3.8)	3.0 (S.D. ± 1.0)

informed consent. The demographic data were analyzed (Table).

Patient examinations included slit-lamp biomicroscopy, ophthalmoscopy, tonometry as measured with a Goldmann tonometer, blood-pressure measurement in a sitting position, and perimetry with the Octopus 201 G1 program.[18] All visual field tests were performed by the same perimetrist, using the same instrument under uniform conditions. The patients were repeatedly urged to report any side effects of the treatment.

All patients had undergone previous ophthalmic examinations and were experienced with Octopus visual field testing before they entered the study. After the decision to include a patient in the study was made, all previous treatment was discontinued for at least two weeks. At the end of this washout period, the first examination was performed. The results of this examination were the baseline readings to which all the other readings were referred. Bilateral treatment with either betaxolol 0.5% or timolol 0.5% twice daily was then initiated. Patients were assigned to a treatment group in a random, double-masked fashion.

Patients were reexamined three, six, 12, and 18 months after initiation of the treatment. All these examinations included measurement of intraocular pressure, visual field, and blood pressure.

To evaluate the evolution of the visual fields, regressions of the mean sensitivities[19] vs time were calculated for each patient. The mean sensitivity was determined for each eye separately, as well as for both eyes. The slopes of these regression lines were compared between treatment groups by use of the Mann Whitney U test. The degree of freedom was the number of patients, less one, for comparing both the separate values as well as the averaged values.

Results

Forty patients entered the study, and 36 patients completed the 18-month treatment period. Two patients in the timolol-treated group discontinued treatment for personal reasons. One patient in the timolol-treated group dropped out because of a newly developed bronchial asthma. Another patient in the betaxolol-treated group discontinued treatment because of a stinging sensation upon eyedrop instillation. Therefore, the analysis was based on 72 eyes of 36 patients (with 19 patients in the betaxolol-treated group and 17 patients in the timolol-treated group).

Because the patients were randomly assigned to groups, the variables examined in the study were not entirely identical in the two treatment groups (Table). The groups were similar in baseline intraocular pressure and age. The visual fields after the washout period were slightly (but not statistically significant) better in the betaxolol-treated group than they were in the timolol-treated group. The betaxolol-treated group was somewhat more heterogeneous. Both groups included patients with more diffuse defects as well as more localized defects.

Both drugs reduced intraocular pressure significantly ($P < .001$). The decrease in intraocular pressure was more pronounced in the timolol-treated group than in the betaxolol-treated group (Fig. 1). This difference, however, was not statistically significant.

The influence of treatment was beneficial to visual fields in both groups in the first six months. Thereafter, most visual fields became stable or deteriorated. To quantify the time trend, linear regressions of the mean sensitivities and average mean sensitivity against time were calculated for each patient. The slopes of these regressions were compared between betaxolol-treated and timolol-treated groups. These analyses showed a more favorable time trend in the betaxolol-treated group than in the timolol-treated group (Fig. 2). The Mann Whitney U test disclosed the following P values: $P = .116$ for right eyes, $P = .040$ for left eyes, and $P = .041$ for the average of right and left eyes.

The treatment effect on the visual fields did not correlate to the initial intraocular pressure or to the decrease in intraocular pressure. Furthermore, no relationship between initial visual fields and visual field changes was observed during the treatment.

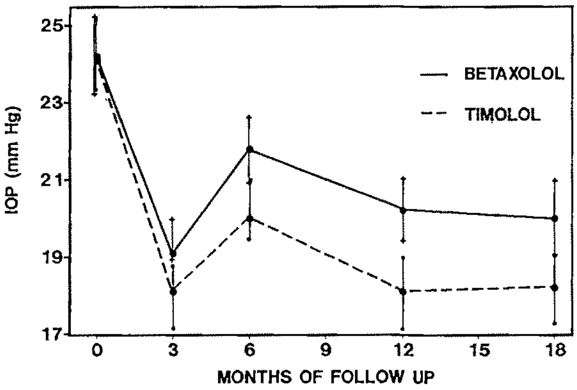

Fig. 1 (Messmer, Flammer, and Stümpfig). Influence of betaxolol and timolol on intraocular pressure during the 18-month follow-up period. IOP indicates intraocular pressure.

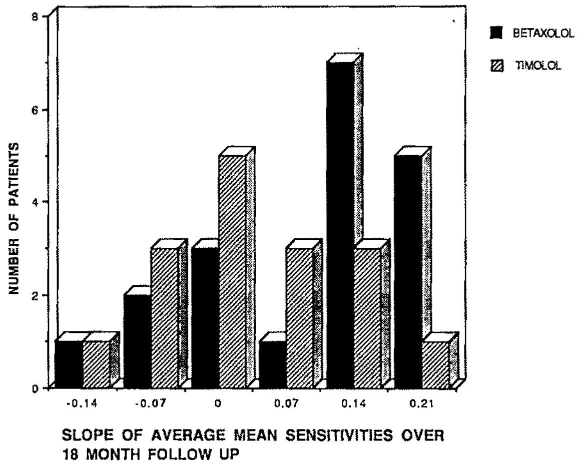

Fig. 2 (Messmer, Flammer, and Stümpfig). Distribution of slopes of the averaged mean sensitivities for the betaxolol-treated and timolol-treated groups. Positive slopes indicate improvement; negative slopes indicate deterioration of the visual field.

Discussion

The treatment of patients with glaucoma is still a challenge. It is well known that not all patients with increased intraocular pressure develop visual field defects. Conversely, visual field progression, despite well-controlled intraocular pressure, can be observed. The treatment with beta-blockers is well established. Currently, beta-blockers are selected on the basis of the frequency of side effects. Because the purpose of the treatment was to maintain visual function, we compared the influence of the betaxolol and timolol treatment on the visual fields.

We found that timolol tended to reduce intraocular pressure better than betaxolol and that betaxolol tended to have a better influence on the visual fields than did timolol. However, these observations were made on the basis of relatively few and selected patients. All patients had early types of glaucomatous damage, and the intraocular pressure was increased, allowing a single treatment. Nevertheless, it is interesting that the visual function of these patients seemed to improve during treatment. This effect cannot simply be attributed to a learning process, as our patients had undergone many visual field examinations before they entered the study. Such a treatment effect has previously been described.[20,21] However, it and micromorphometric features in enucleated cases.[13,14] We also showed that a statistical model comprising tumor volume, location, and acoustic scatterer concentration can be used to predict survival after enucleation.[15] In this study we extend this model to compare survival of patients treated with radiotherapy (cobalt-60 brachytherapy) or enucleation and develop a model to determine survival estimates for individual classes of patients.

Patients and Methods

Ultrasonic tissue characterization became available for the evaluation of ocular tumors seen at New York Hospital–Cornell Medical Center as early as 1979. Since then, 1,375 scan sessions have been performed on 570 patients with tumors of all kinds. Follow-up data were obtainable on 62 patients with uveal melanoma whose eyes were enucleated. One hundred forty patients were treated with cobalt-60 brachytherapy. Pretreatment scans and posttreatment follow-up data were obtained on 74 of these patients (of the remaining patients, ultrasonic tissue characterization data were not obtained on 55 patients before treatment, four patients did not have adequate follow-up, and seven were excluded because cobalt-60 plaque was used in combination with other treatment modalities). Patient survival subsequent to treatment was determined from medical records, contact with patients or their families, and death certificates. Extensive skip tracing was used to obtain well-documented follow-up.

Before treatment with cobalt-60 plaque or enucleation, patients were scanned by diagnostic ultrasonography using the immersion technique. Tumor height and base dimensions were determined during the ultrasonic examination. The ultrasonic system operated at a center frequency of 10 MHz with a 15-dB band width of 10 MHz. Data were digitized at a sample rate of either 50 or 100 MHz.

Tissue characterization was performed by the normalized power spectrum method. Mean acoustic scatterer diameter and CQ^2 (the product of scatterer concentration, C; and the square of relative impedance, Q) were then computed from the slope (dB/MHz) and 0-MHz intercept (dB) of the linear best fit of the power spectrum.[14] On the basis of the simplifying assumption that relative impedance is close to unity, CQ^2 will generally be referred to as acoustic concentration. The value of CQ^2 is presented in decibel form ($10 \log[CQ^2]$) in units of scatterers per cubic millimeter. Estimated tumor volumes were computed from tumor base and height dimensions using an ellipsoidal solid model.[16]

The relationship between clinical factors, ultrasonic tissue characteristics, and patient survival were examined using univariate and multivariate statistical techniques. Kaplan-Meier survival analysis, a univariate technique, was used for comparison of study subpopulations. The Cox multiple risk model,[17] a multivariate technique for discrete and continuous variables, was used for assessment of risk factors and their interdependencies. A generalization of the Cox model, the Andersen-Gill model,[18] was used along with graphic analysis of residuals to examine model validity. Multiple regression analysis, where the logarithm of survival time is a linear function of the independent variables, was used for the predictive model.[19] In these analyses, patient deaths caused by metastatic disease were considered terminal. All others, including patient deaths of other or indeterminate causes, were considered censored.

The models assume radiation doses applied to individual patient's tumors are therapeutically equivalent. Target apex dose from the cobalt-60 applicator was 8,000 to 10,000 mGy. However, total tumor dose varied according to different tumor sizes, changing plaque activity, and application time.

Results

Survival statistics for the patient population stratified by treatment, tumor volume, location, and backscatter characteristics were analyzed (Table 1). The results indicated that survival decreased with tumor size and with ciliary body involvement. The results also suggested poorer survival for patients treated with enucleation than for patients treated with brachytherapy, but this will later be shown to have been caused by the covariate factor of tumor size.

The study population was stratified by volume for each treatment. Kaplan-Meier survival statistics (Table 2) suggested that patients with small tumors (<250 mm^3) who were treated with brachytherapy had a higher survival rate than those whose eyes were enucleated (92% vs 74%, five-year survival), although statistically

TABLE 1
AGGREGATE SURVIVAL STATISTICS

FACTOR	NO. OF PATIENTS	DIED	FIVE-YEAR SURVIVAL (%)	SCORE	D	P VALUE
Volume (mm^3)						
< 250	49	8	85.8	11.5	—	—
250-750	50	14	75.9	−1.3	—	—
750-1,500	24	8	77.3	2.8	—	—
> 1,500	13	7	34.1	−43.6	12.44	.006
Location						
Posterior	111	27	81.4	5.4	—	—
Ciliary body	25	10	50.3	−23.8	6.83	.009
Treatment						
Enucleation	62	22	69.8	−8.7	—	—
Brachytherapy	74	15	81.5	7.3	3.41	.065
10Log scatterer concentration						
< −14	69	19	76.1	−1.25	—	—
> −14	67	18	75.9	1.28	0.09	.769
Scatterer diameter (μm)						
< 70	67	22	78.7	−1.24	—	—
> 70	69	15	73.0	1.20	0.08	.777

this was only moderately significant (P = .113). For patients with intermediate-sized lesions (250 to 750 mm^3 and 750 to 1,500 mm^3), no significant differences in survival were found between the two treatments. Interestingly, the five-year survival for patients with enucleated eyes was nearly constant for tumors having volumes of less than 1,500 mm^3, whereas the percentiles for patients treated with radiotherapy decreased from 92% to 75% to 60% for tumor volumes less than 250 mm^3, 250 to 750 mm^3, and 750 to 1,500 mm^3, respectively. Brachytherapy was not used in patients with tumors greater than 1,500 mm^3 in size (the largest group). The five-year survival percentile for the patients with enucleated eyes in this group was 34%.

Because radiotherapy appeared to be effective in terms of survival for tumors less than 250 mm^3 in size and had the added benefit of preserving visual function, we restricted the remainder of our analysis to the group of patients with intermediate-sized tumors (250 to 1,500 mm^3).

A Cox model was developed for intermediate-sized tumors for each treatment group on the basis of tissue scatterer characteristics and tumor location. This multivariate technique assessed the risk of each possible factor, while taking into account the effects of other cofactors (Table 3). The results of this analysis indicate that risk is related primarily to the diameter of scatterer and tumor location for the subgroup of patients with enucleated eyes. For the brachy-

TABLE 2
COMPARISON OF SURVIVAL RATES FOR ENUCLEATION AND BRACHYTHERAPY WITH STRATIFICATION BY TUMOR VOLUME

	ENUCLEATION			BRACHYTHERAPY			
GROUP (MM^3)	NO. OF PATIENTS	DIED	FIVE-YEAR SURVIVAL (%)	NO. OF PATIENTS	DIED	FIVE-YEAR SURVIVAL (%)	P VALUE
< 250	17	5	74.0	32	3	92.2	.110
250-750	14	4	76.6	36	10	75.4	.635
750-1,500	18	6	82.2	6	2	60.0	.431
> 1,500	13	7	34.1	0	0	—	—

TABLE 3
COX MULTIVARIATE RISK MODEL

FACTOR	χ^2	P VALUE	R^2	β	STANDARD ERROR OF β
			Enucleation		
Diameter	7.38	.0066	.243	−.3037	.1118
Concentration	0.07	.7880	.003	−.0238	.0088
Location	6.63	.0100	.224	1.978	.7661
Model	14.76	.0020	.391	—	—
			Brachytherapy		
Diameter	3.07	.0799	.106	−.0878	.0502
Concentration	5.58	.0182	.177	−.2525	.1069
Location	5.32	.0211	.170	1.619	.7018
Model	10.91	.0122	.296	—	—

therapy-treated eyes, concentration of scatterer and tumor location were the most important risk factors. Both models were found to be statistically significant (enucleation, $P = .002$; brachytherapy, $P = .012$). Examination of residuals from the Cox and equivalent Andersen-Gill models showed no basic violations of model assumptions or strong leverage effects, thus confirming model adequacy and accuracy.

The data were further analyzed by use of a multiple regression model appropriate for censored data (Table 4). This is a predictive model in which the logarithm of survival time is a linear function of the risk factors of tumor location, scatterer diameter, and scatterer concentration. Survival rate was also calculated using this model (Figs. 1 through 4).

The multiple regression model permits computation of predicted patient survival for patients with tumors with calculated volumes of 250 to 1,500 mm^3 for either treatment, given tumor location and backscatter characteristics. The 95% certainty ranges for the survival rates were determined (Fig. 4). Uncertainty bounds for survival estimates for the alternate treatments show regions of overlap and nonoverlap for a specific value of acoustic backscatter properties. For patients with certain tumors, predicted survival would be statistically different for the alternate treatments; for others it would not. For example, a posteriorly located tumor with scatterer diameter of 69 μm and concentration of $10^{-0.96}$ mm^{-3} would have a predicted survival of 147 months (range, 112 to 195 months) with enucleation and 132 months (range, 105 to 166 months) with brachytherapy, where the number in parentheses indicates the 95% confidence interval. For such a case, there does not appear to be any statistically meaningful difference in predicted survival for the alternative treatments. Cases in which no statistical difference in predicted survival exists between the alternative therapies would fall near the line of interception of the appropriate survival surfaces. In contrast, in a case with scatterer diameter of 59 μm and concentration of $10^{-0.80}$ mm^{-3}, the survival estimates are 32 months (range, 19 to 53 months), and 123 months (range, 91 to 166 months) for enucleation and brachytherapy, respectively, a statistically significant difference.

Discussion

We determined that differences in the survival rate of patients with intermediate-sized uveal melanomas who were treated with enu-

TABLE 4
MULTIVARIATE REGRESSION MODEL

FACTOR	β	STANDARD ERROR OF β	*T*-TEST	P VALUE	SEQUENTIAL R^2
		Enucleation			
Y-intercept	−2.237	.5848	—	—	—
Diameter	.0682	.0088	7.27	<.0001	.317
Concentration	−.000154	.00958	−0.02	.9873	.326
Location	−.6414	.0801	−8.00	<.0001	.795
		$F = 36.17$, $P < .001$			
		Brachytherapy			
Y-intercept	1.847	.3262	—	—	—
Diameter	.0096	.0049	1.97	.0562	.007
Concentration	.0406	.0073	5.60	<.0001	.410
Location	−.1589	.0860	−1.85	.0723	.459
		$F = 10.75$, $P < .001$			

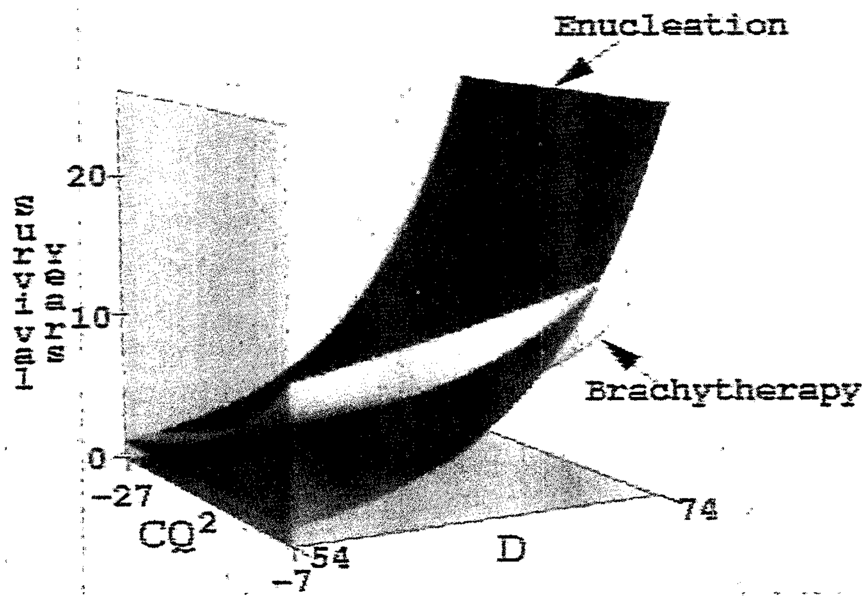

Fig. 1 (Coleman and associates). Contour plot representing predicted survival of enucleated vs brachytherapy-treated posterior melanomas. Survival (vertical axis) is a function of mean scatterer diameter and concentration, which together define the horizontal plane.

cleation or Cobalt-60 brachytherapy can be modeled using a multivariate approach with the following quantifiable factors: (1) tumor acoustic scatterer characteristics, (2) tumor volume measurement, and (3) tumor location. The models demonstrate that differences exist in the response of uveal melanoma to alternate forms of treatment and that these differences can be identified by noninvasive means. The models were extended to obtain predictive equations with confidence intervals that can be used to compare estimated survival for the alternate treatments in individual cases.

The models' clinical factors, estimated tumor volume and location, have previously been shown to correlate with patient survival.[6-8] The acoustic scatterer factors have been shown to correlate to histopathologic and micromorphometric features of the tumor, as well as with patient survival in cases that required enucleation of eyes.[13,15]

The acoustic backscatter factors used in the models are related to the spatial distribution, size, and density of tissue inhomogeneities, and are primarily sensitive to tissue structures ranging from about 25 to 75 μm in cross section. They may be considered analogous to statistical measures of cell distribution patterns as seen through an optical microscope, rather than assessments of the characteristics of individual cells.

Although it is possible that analysis of histo-

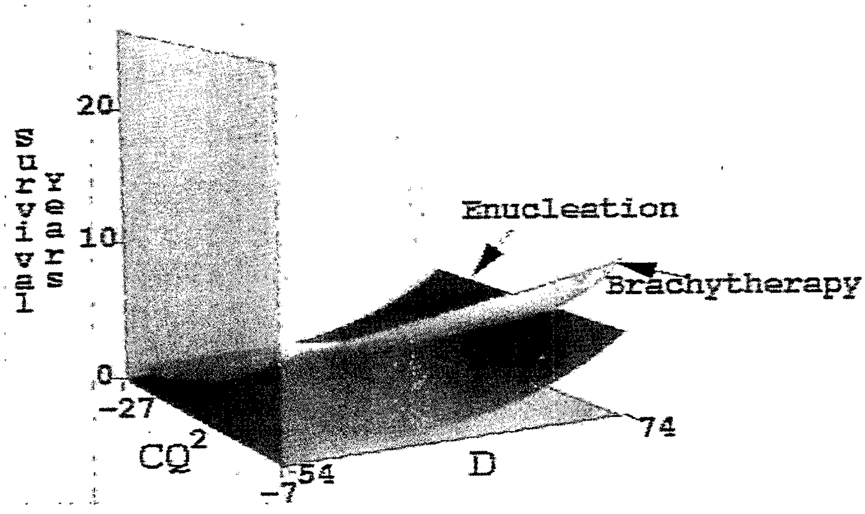

Fig. 2 (Coleman and associates). Contour plot representing predicted survival of enucleated vs brachytherapy-treatedmelanomasinvolving the ciliary body.

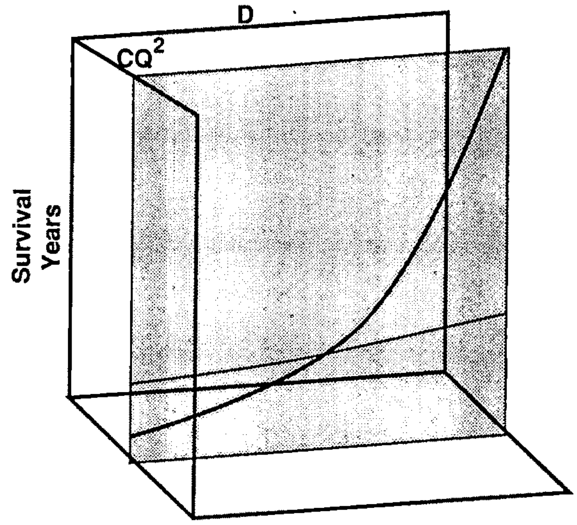

Fig. 3 (Coleman and associates). Orthogonal planes cutting across three-dimensional projections define survival curves as functions of either scatterer diameter or concentration.

pathologic characteristics could provide a statistically significant assessment of patient survival as is suggested by data from cases of enucleated eyes,[15] it would require an invasive technique. Fine-needle biopsy procedures could be used if a sufficiently representative sample of the tumor would be obtained. However, at present, biopsy of intraocular tumors is generally regarded as unwarranted because of risks of tumor seeding or hemorrhage and is reserved for situations in which the diagnosis is uncertain. The current model factors described in this study may be obtained noninvasively before treatment selection and can evaluate the entire tumor volume.

In this study, survival rates for patients with uveal melanomas of intermediate size were estimated. Statistically significant differences in survival were found between enucleated and brachytherapy-treated eyes for certain combinations of tumor acoustic characteristics, volume, and location. The usefulness and accuracy of the survival estimates were bound by the error associated with the model coefficients. Larger study populations would allow us to define model variance better and improve survival estimates. Also, any prospective use of the model for treatment planning would be predicated on correct initial diagnosis of uveal malignant melanoma. We currently use an ultrasonic tissue characterization diagnosis protocol to determine tumor type and subtype; however, our database does not include sufficient data to subclassify masquerading lesions such as leiomyoma (diktyoma) or melanocytoma.[13] Additionally, the model cannot be used for previously treated tumors because treatment modifies tumor acoustic characteristics.

Our model using ultrasonic tissue characterization techniques provides a unique method for comparing the efficacies of different forms of melanoma treatment and may allow ocular melanoma treatment to be tailored to maximize individual patient survival.

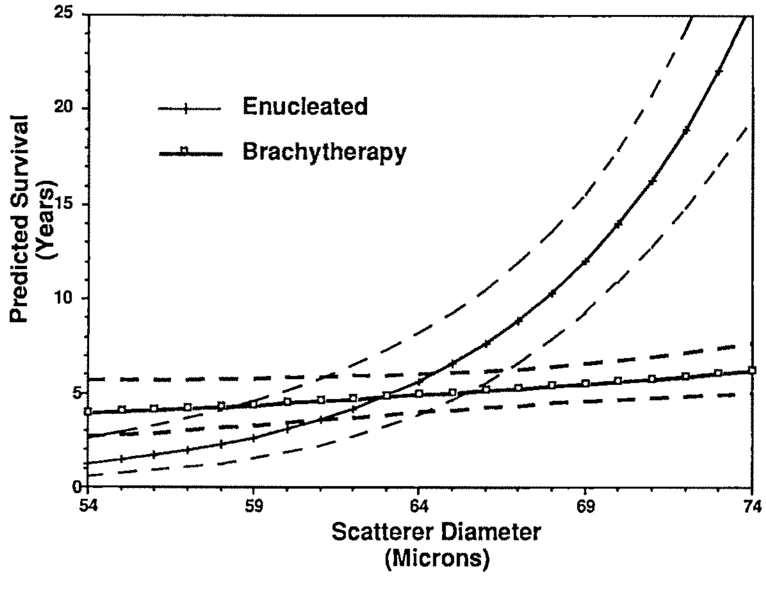

Fig. 4 (Coleman and associates). The plot demonstrates the relationship defined in Figure 1 for posteriorly located tumors having a scatterer concentration of −17 (the average for the study population) and includes the 95% confidence bounds. For each patient and each of the two possible treatment modalities, a measured scatterer concentration and diameter (combined with volume and location) will define a point (with known statistical uncertainty) within the three-dimensional projection.

References

1. Manschot, W. A., and van Strik, R.: Is irradiation a justifiable treatment of choroidal melanoma? Analysis of published results. Br. J. Ophthalmol. 71:348, 1987.

2. Gass, J. D. M.: Comparison of prognosis after enucleation vs cobalt-60 irradiation of melanomas. Arch. Ophthalmol. 103:916, 1985.

3. Markoe, A. M., Brady, L. W., Shields, J. A., Augsburger, J. J., Micaily, B., Damsker, J. J., Day, J. L., and Gamel, J. W.: Malignant melanoma of the eye. Treatment of posterior uveal lesions by Co-60 plaque radiotherapy versus enucleation. Radiology 156:801, 1985.

4. Augsburger, J. J., Gamel, J. W., Sardi, V. S., Greenberg, R. A., Shields, J. A., and Brady, L. W.: Enucleation versus cobalt plaque radiotherapy for malignant melanomas of the choroid and ciliary body. Arch. Ophthalmol. 104:655, 1986.

5. Augsburger, J. J., Gamel, J. W., Lauritzen, K., and Brady, L. W.: Cobalt-60 plaque radiotherapy vs enucleation for posterior uveal melanoma. Am. J. Ophthalmol. 109:585, 1990.

6. Seddon, J. M., Gragoudas, E. S., Egan, J. M., Glynn, R. J., Howard, S., Fante, R. G., and Albert, D. M.: Relative survival rates after alternative therapies for uveal melanoma. Ophthalmology 97:769, 1990.

7. Flocks, M., Gerende, J. H., and Zimmerman, L. E.: The size and shape of malignant melanomas of the ciliary body in relation to prognosis and histologic characteristics. A statistical study of 210 tumors. Trans. Am. Acad. Ophthalmol. Otolaryngol. 59:740, 1955.

8. McLean, I. W., Foster, W. D., and Zimmerman, L. E.: Prognostic factors in small malignant melanomas of the choroid and ciliary body. Arch. Ophthalmol. 95:48, 1977.

9. Weinhaus, R. S., Seddon, J. M., Albert, D. M., Gragoudas, E. S., and Robinson, N.: Prognostic factor study of survival after enucleation for juxtapapillary melanomas. Arch. Ophthalmol. 103:1673, 1985.

10. Gamel, J. W., McLean, I., Greenberg, R. A., Naids, R. M., Folberg, R., Donoso, L. A., Seddon, J. M., and Albert, D. M.: Objective assessment of malignant potential of intraocular melanomas with standard microslides stained with hematoxylin-eosin. Hum. Pathol. 16:689, 1985.

11. Donoso, L. A., Augsburger, J. J., Shields, J. A., Greenberg, R. A., and Gamel, J.: Metastatic uveal melanoma. Correlation between survival time and cytomorphometry of primary tumors. Arch. Ophthalmol. 104:76, 1986.

12. Seddon, J. M., Polivogianis, L., Hseih, C.-C., Albert, D. M., Gamel, J. W., and Gragoudas, E. S.: Death from uveal melanoma. Number of epithelioid cells and inverse SD of nucleolar area as prognostic factors. Arch. Ophthalmol. 105:801, 1987.

13. Coleman, D. J., Lizzi, F. L., Silverman, R. H., Rondeau, M. J., Smith, M. E., and Torpey, J. H.: Acoustic biopsy as a means for characterization of intraocular tumors. In Henkind, P. (ed.): Acta. XXIV International Congress of Ophthalmology, vol. 1. Philadelphia, J. B. Lippincott Company, 1983, pp. 115–118.

14. Feleppa, E. J., Lizzi, F. L., Coleman, D. J., and Yaremko, M. M. Diagnostic spectrum analysis in ophthalmology. A physical perspective. Ultrasound Med. Biol. 12:623, 1986.

15. Coleman, D. J., Silverman, R. H., Rondeau, M. J., Lizzi, F. L., McLean, I. W., and Jakobiec, F. A.: Correlations of acoustic tissue typing of malignant melanoma and histopathologic features as a predictor of death. Am. J. Ophthalmol. 110:380, 1990.

16. Kidd, M. N., Lyness, R. W., Patterson, C. C., Johnson, P. B., and Archer, D. B.: Prognostic factors in malignant melanoma of the choroid. A retrospective survey of cases in Northern Ireland between 1965 and 1980. Trans. Ophthalmol. Soc. U.K. 105:114, 1986.

17. Cox, D. R.: Regression models and life-tables. J. R. Stat. Soc. 34:187, 1972.

18. Therneau, T. M., Grambsch, P. M., and Fleming, T. R.: Martingale-based residuals for survival models. Biometrika 77:147, 1990.

19. Schmee, J., and Hahn, G. J.: A simple method for regression-analysis with censored data. Technometrics 21:417, 1979.

Hemianopsia From Occipital Lobe Abscess After Dental Care

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Melvin G. Alper, M.D., and Jonathan C. Horton, M.D.

We treated four patients who developed a homonymous hemianopsia from a bacterial abscess in the occipital lobe of the brain. All four patients were treated successfully by surgical drainage of the abscess and administration of parenteral antibiotics for at least six weeks. Despite cure of the brain abscess, each patient was left with a permanent residual homonymous visual field defect. Cultures from the abscess fluid in three of the four patients grew oral flora. Moreover, each patient had a history of dental care two to four weeks before the onset of visual symptoms. A history of recent dental treatment in a patient with a new hemianoptic field defect should alert the ophthalmologist to the possibility of a bacterial abscess in the occipital lobe.

Pyogenic abscess of the occipital lobe is an uncommon cause of hemianoptic visual loss. The infection is usually caused by hematogenous dissemination of bacteria from a remote primary site. The chance of survival is improved by rapid diagnosis. Since the introduction of computed tomography, the mortality rate from parenchymatous brain abscess has decreased from 40% to less than 5%.[1]

We treated four patients with bacterial abscess of the occipital lobe. Each patient developed visual symptoms several weeks after dental treatment. We suggest that transient bacteremia during dental manipulation provided the inoculum for the brain abscess.

Case Reports

Case 1

A 13-year-old girl had a five-day history of headache and nausea, and complained of spots moving before her eyes. She had a fever of 37.7 C but results of her physical examination were otherwise normal. She was treated with analgesics and discharged. The girl had a history of chronic headache that began four years earlier. At that time, results of electroencephalography and computed tomography were normal and she was considered a migraineur.

Twelve hours later, the patient was admitted to a hospital because of persistent vomiting and a fever of 38.9 C. A computed tomographic scan obtained without contrast was normal. A lumbar puncture performed the next day yielded clear colorless fluid with an opening pressure of 300 mm H_2O. The glucose concentration was 55 mg/dl and the protein concentration was 120 mg/dl. There were 701 white blood cells/mm^3, of which 90% were polymorphonuclear leukocytes. No organisms were found on Gram staining. The patient was treated empirically with intravenously administered ceftriaxone for meningitis. Computed tomography with intravenous contrast was performed the next day. It disclosed a faint pattern of ring enhancement in the right occipital lobe. Subsequently, the patient's visual fields were tested and a left homonymous hemianopsia was discovered.

When the patient was transferred the next day to our institution, her visual acuity was 20/20 in both eyes without correction. She had a dense left homonymous hemianopsia as determined by confrontation testing. Magnetic resonance imaging showed a bilocular mass in

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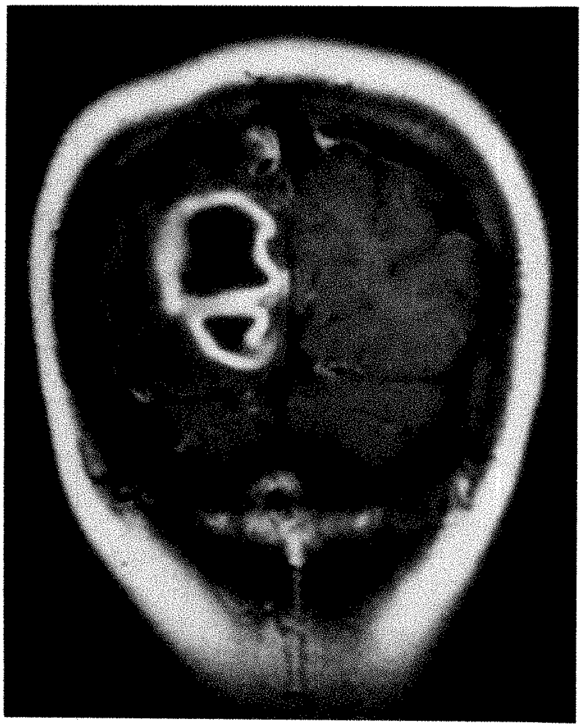

Fig. 1 (Wohl and associates). Coronal T_1-weighted magnetic resonance image showing a bilocular lesion in the right occipital lobe in Patient 1. A prominent ring pattern of enhancement is visible after gadolinium administration.

the right occipital lobe. Ring enhancement was observed after administration of gadolinium (Fig. 1). Intravenously administered penicillin, metronidazole, and nafcillin were substituted for ceftriaxone. The next day, the mass was tapped through a right occipital burr hole and 10 ml of foul purulent material drained spontaneously. All smears and cultures were negative. Echocardiography showed mitral valve prolapse but no evidence of endocarditis.

For the next two weeks, the patient continued to have intermittent headaches and fluctuating fevers. A follow-up scan showed no diminution in the occipital lobe abscess. The patient was taken back to the operating room and 30 ml of pus was aspirated. After this procedure, the patient improved rapidly and was discharged from the hospital a week later. An eight-week course of parenteral penicillin and nafcillin, plus orally administered metronidazole, was completed at home. A year later, the patient had an incongruous left lower quadrantic field defect.

After the diagnosis of occipital lobe abscess was established, further questioning disclosed that the patient's teeth had been cleaned by a dental hygienist four weeks before the onset of visual symptoms. Alginate impressions of the teeth had also been prepared to assist in the planning of orthodontia care. At the time of this procedure, a dentist examined the child's teeth and observed only mild gingival disease. She had seven class-1 fillings and no caries.

Case 2

A 48-year-old man consulted his ophthalmologist a few days after developing a severe headache and multiple, evanescent white stars in his right visual hemifield. On examination, the visual acuity was correctable to 20/20 in both eyes. A dense right homonymous paracentral scotoma was mapped with a Goldmann perimeter. Contrast-enhanced computed tomography disclosed a poorly defined left occipital mass with surrounding edema; no ring enhancement was observed. A malignant tumor was suspected. The patient was treated with phenytoin and dexamethasone and his symptoms improved. An operation was scheduled for the next week.

At craniotomy, an occipital lobe abscess was discovered. Gram staining showed many gram-positive cocci. Laboratory cultures grew abundant colonies of *Streptococcus milleri*, a member of the viridans group. Results of ultrasonography of the heart were normal. The patient was treated with intravenously administered metronidazole and penicillin but failed to improve. Twelve days later, he developed confusion, alexia, and a complete right homonymous hemianopsia. Another craniotomy was performed to evacuate the occipital lobe abscess completely. After six more weeks of treatment with intravenously administered metronidazole and penicillin, the patient was discharged from the hospital. Two years later the patient had a residual right homonymous hemimacular scotoma.

While the patient was recovering from his first craniotomy, it was learned that a routine dental prophylaxis had been administered two weeks before the onset of visual symptoms. After this history was obtained, the plaque on the patient's teeth was scraped and cultured. *Streptococcus milleri* was successfully isolated among the organisms constituting the oral flora.

Case 3

A 44-year-old man with a 25-year history of migraine sought an emergency consultation for

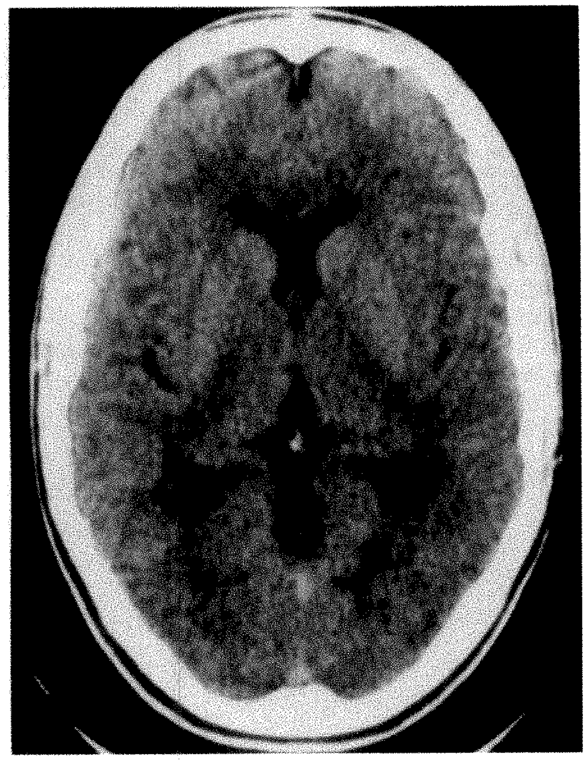

Fig. 2 (Wohl and associates). Axial computed tomographic scan in Patient 3 is unremarkable except for an area of low density just posterior to the occipital horn of the left lateral ventricle.

severe headache. The headache was preceded by intense lights that flashed in the right upper quadrant of his visual field. On examination, the visual acuity was 20/20 in both eyes with correction. A right homonymous superior visual field defect was found with confrontation testing. Computed tomography showed a subtle area of hypodensity in the left occipital lobe consistent with infarct or edema (Fig. 2). This impression was confirmed by a magnetic resonance scan that disclosed an increased bright signal in this region on T_2-weighted images (Fig. 3). Migraine complicated by vascular infarction was diagnosed and the patient was treated with propranolol hydrochloride, aspirin, and analgesics.

At home, the patient continued to experience frequent headaches. Eleven days later he was mildly confused and febrile (39.4 C). He was taken to the hospital emergency room, where a lumbar puncture was performed. The fluid contained 1,230 white blood cells/mm^3 and the protein concentration was 149 mg/dl. The patient was treated with intravenously administered ampicillin, cefotaxime, and metronidazole. A magnetic resonance scan showed a left occipital lobe lesion with ring enhancement after gadolinium administration (Fig. 4). Several days later, the lesion was aspirated and 18 ml of pus was removed. The cultures grew microaerophilic streptococci. Results of ultrasonography of the heart were normal. The patient responded well to a six-week course of parenteral antibiotics. A year later he had a small permanent defect in the periphery of the upper right visual field.

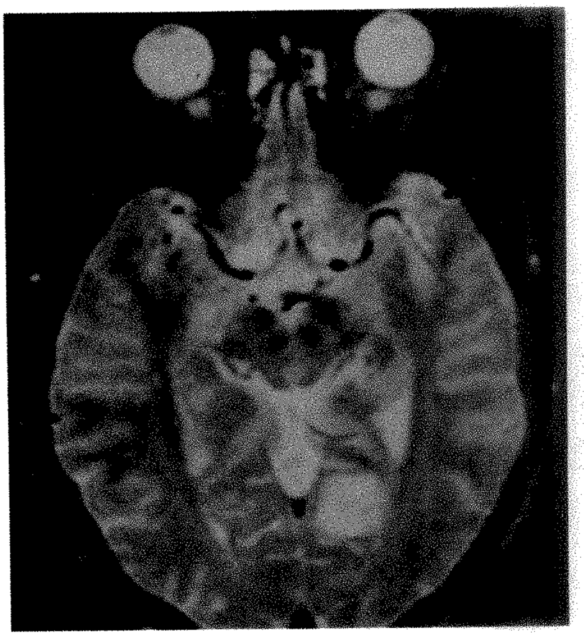

Fig. 3 (Wohl and associates). Axial T_2-weighted magnetic resonance image in Patient 3 shows an area of bright signal representing tissue edema posterior to the occipital horn of the left lateral ventricle. This scan was obtained the same day as the computed tomographic scan illustrated in Figure 2.

The patient later recounted that two to three weeks before the abrupt onset of his visual symptoms and headache he had undergone an endodontic (root-canal) operation.

Case 4

A 60-year-old woman observed the onset of blurred vision two days after developing headache and fever. She was examined by her internist who prescribed erythromycin and acetaminophen by mouth. The next day she was brought to the hospital emergency room in a confused and agitated condition. Her temperature was 39 C and her neck was slightly stiff. On cardiac auscultation, a midsystolic click was heard. The visual acuity was 20/20 in both eyes with correction. A left homonymous hemianop-

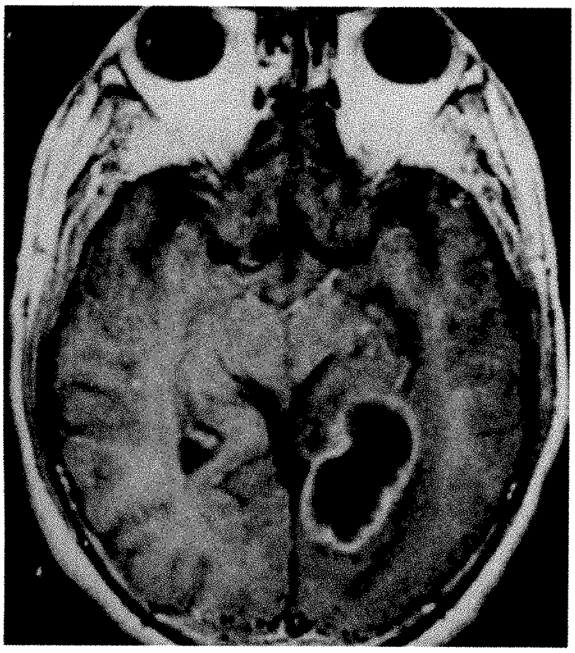

Fig. 4 (Wohl and associates). Axial T_1-weighted magnetic resonance image with gadolinium discloses a ring enhancing lesion in the left occipital lobe. This scan was obtained 11 days after the scan shown in Figure 3.

sia was detected by confrontation testing at the bedside in the emergency room.

Computed tomography showed an area of low density in the right occipital lobe. With contrast administration, a ring of enhancement was evident. The next day the patient underwent a right occipital craniotomy and 15 ml of pus was drained from an abscess cavity. Cultures were positive for viridans group streptococci. Echocardiography demonstrated mitral valve prolapse but no vegetations on the cardiac valves. The patient completed a course of six weeks of intravenously administered penicillin in the hospital. Four years later, she had a persistent left inferior homonymous quadrantanopsia.

A review of her history later disclosed that 12 days before the onset of blurred vision, the patient had received an annual dental examination and prophylaxis.

Discussion

We treated four patients who developed hemianopsia caused by an occipital lobe abscess after receiving routine dental care. The phenomenon of transient bacteremia after tooth extraction was first described by Okell and Elliott[2] more than a half century ago. Using standard blood culture techniques, they found bacteremia in 34% of patients with no detectable gum disease. In a recent study, bacteremia was found by the lysis-filtration method in 100% of patients after tooth extraction.[3] Less invasive oral procedures such as root-canal operations, scaling, and filling of teeth are also associated with transient bacteremia.[3,4] Even relatively minor procedures such as dental prophylaxis can produce bacteremia.[5,6] Silver, Martin, and McBride[7] documented bacteremia in 44% of their patients after toothbrushing. The actual frequency and amount of bacterial seeding depends on the severity of existing gingival and periodontal disease and also on the vigor of oral prophylaxis.[7]

In our patients, several lines of evidence implicated previous dental treatment as the cause of brain abscess. The interval of two to four weeks that elapsed between dental care and the onset of visual symptoms corresponds to the amount of time required for the development of a brain abscess.[8] No other recent procedure or source was found to explain the brain abscess in our patients. Moreover, dental flora grew from the abscesses' fluid in all three patients with positive cultures. In two patients, the bacterial species were from the viridans group streptococci. The oral cavity is heavily colonized with these organisms. Heimdahl and associates[3] reported that in patients with positive blood cultures after tooth extraction, 85% of isolates were members of the viridans group streptococci. In our third patient, the organisms cultured from the brain abscess were identified as microaerophilic streptococci organisms. These obligate anaerobes are common inhabitants of the periodontal space. Finally, in our second patient *S. milleri* grew from the brain abscess material and was also isolated from the patient's own dental flora.

The association between dental treatment and cerebral abscess has been reported previously. In 1945, Haymaker[9] described eight cases of brain abscess after tooth extraction. Since that initial publication, a number of studies and individual case reports have confirmed an etiologic connection between dental procedures and brain abscess.[10-14] A dental source accounts for at least 4% to 7% of all pyogenic brain abscesses.[15,16] The true percentage may actually be higher, inasmuch as no source is identified in most cases of brain abscess. A previous case report described hemianopsia from a cerebral abscess after dental treatment.[17]

Two of our patients had mitral valve prolapse, a common and usually benign condition occurring in at least 5% of the population.[18] Mitral valve prolapse has a 5.3 to 8.2 increase in the relative risk of infective endocarditis after dental procedures.[19] The American Heart Association advises prophylactic antibiotic coverage for all dental procedures in patients with mitral valve prolapse accompanied by valvular regurgitation.[20] The current recommended treatment regimen is amoxicillin, 3.0 g orally one hour before the procedure and 1.5 g six hours after the initial dose. Patients allergic to penicillin or amoxicillin may be treated with erythromycin or clindamycin.

It is unclear whether mitral valve prolapse was an incidental finding in our patients, or whether it contributed to cerebral abscess formation. We found no evidence for bacterial endocarditis in any of our patients; blood cultures and results of echocardiography were negative. However, echocardiography often fails to detect colonization of the cardiac valves in endocarditis.

After bacterial seeding of the brain, a period of two to four weeks is required for maturation of an encapsulated pyogenic abscess.[8] Abscess formation is preceded by a period of early cerebritis. During this stage many patients are asymptomatic. About 50% of patients have intermittent headache or fever. Eventually brain necrosis or mass effect is sufficient to induce focal neurologic signs. At this point, patients usually seek medical consultation and computed tomographic magnetic resonance study is performed. Magnetic resonance imaging is more sensitive than computed tomography in detecting the cerebritis that precedes the formation of a frank abscess. The administration of contrast material is helpful because the capsule of a mature abscess shows a distinctive pattern of rim enhancement. Whether magnetic resonance or computed tomography is used to image the brain, it is important to be aware that an abscess can be confused with either tumor or infarct, especially in the early stages of capsule formation.[21,22] Correct diagnosis was delayed in several of our patients because the cerebral lesion lacked typical features of brain abscess on initial neuroradiologic study. Our findings suggest that it may be worthwhile to query patients who have a new hemianoptic disturbance of vision about any dental treatment received during the preceding two to four weeks. In our experience, such information was not volunteered spontaneously. A trip to the dentist several weeks before is easily overlooked and likely to be regarded as irrelevant by a patient suffering from new visual symptoms. If a history of recent dental care is obtained, suspicion should be heightened for occipital lobe abscess. Early recognition of occipital lobe abscess can reduce morbidity and improve outcome. In selected cases, it may be possible to avoid neurosurgical intervention if treatment with antibiotics is initiated promptly.[23,24] Identification of a probable dental source also helps to guide the choice of antibiotic treatment. Antimicrobial treatment should include medications effective against streptococci organisms and other oral flora.

References

1. Rosenblum, M. L., Hoff, J. T., Norman, D., Weinstein, P. R., and Pitts, L.: Decreased mortality from brain abscess since advent of computerized tomography. J. Neurosurg. 49:658, 1978.

2. Okell, C. C., and Elliott, S. D.: Bacteraemia and oral sepsis with special reference to the aetiology of subacute endocarditis. Lancet 2:869, 1935.

3. Heimdahl, A., Hall, G., Hedberg, M., Sandberg, H., Soder, P.-O., Tuner, K., and Nord, C. E.: Detection and quantitation by lysis-filtration of bacteremia after different oral surgical procedures. J. Clin. Microbiol. 28:2205, 1990.

4. Batch, A. L., Pressman, H. L., Schaffer, C., Smith, R. P., Hammer, M. C., Shayegani, M., and Michelson, P.: Bacteremia in patients undergoing oral procedures. Study following parenteral antimicrobial prophylaxis as recommended by the American Heart Association, 1977. Arch. Intern. Med. 148:1084, 1988.

5. Donley, T. G., and Donley, K. B.: Systemic bacteremia following toothbrushing. A protocol for the management of patients susceptible to infectious endocarditis. Gen. Dent. 36:482, 1988.

6. Silver, J. G., Martin, A. W., and McBride, B. C.: Experimental transient bacteraemias in human subjects with clinically heathy gingivae. J. Clin. Periodontol. 6:33, 1979.

7. ———: Experimental transient bacteraemias in human subjects with varying degrees of plaque accumulation and gingival inflammation. J. Clin. Periodontol. 4:92, 1977.

8. Britt, R. H.: Brain abscess. In Wilkins, R. H., and Rengachary, S. S. (eds.): Neurosurgery. New York, McGraw-Hill Book Company, 1985, pp. 1928–1956.

9. Haymaker, W.: Fatal infections of the central nervous system and meninges after tooth extraction. Am. J. Orthod. Oral Surg. 31:117, 1945.

10. Schliamser, S. E., Backman, K., and Norrby, S. R.: Intracranial abscesses in adults. An analysis of 54 consecutive cases. Scand. J. Infect. Dis. 20:1, 1988.
11. Anderson, W. C., and Horton, H. L.: Parietal lobe abscess after routine periodontal recall therapy. J. Periodontol. 61:243, 1990.
12. Marks, P. V., Patel, K. S., and Mee, E. W.: Multiple brain abscesses secondary to dental caries and severe periodontal disease. Br. J. Oral Maxillofac. Surg. 26:244, 1988.
13. Greenwald, A. M., Kaplan, A., and Eisenberg, L.: Central nervous system disease. A dental diagnosis? J. New Jersey Dent. Assoc. 59:55, 1988.
14. Saal, C. J., Mason, J. C., Cheuk, S. L., and Hill, M. K.: Brain abscess from chronic odontogenic cause. Report of case. J. Am. Dent. Assoc. 117:453, 1988.
15. Hollin, S. A., Hayashi, H., and Gross, S. W.: Intracranial abscesses of odontogenic origin. Oral Surg. Oral Med. Oral Pathol. 23:277, 1967.
16. Moss, S. D., Mclone, D. G., Arditi, M., and Yogev, R.: Pediatric cerebral abscess. Pediatr. Neurosci. 14:291, 1988.
17. Guilbert, F., Hochart, G., Mignolet, G., and Christiaens, J. L.: Hemianopsie laterale homonyme d'origine dentaire. Bull. Soc. Ophtalmol. Fr. 74:827, 1974.
18. Savage, D. D., Garrison, R. J., Devereux, R. B., Castelli, W. P., Anderson, S. J., Levy, D., McNamara, P. M., Stokes, J., Kannel, W. B., and Feinleib, M.: Mitral valve prolapse in the general population. I. Epidemiologic features. The Framingham Study. Am. Heart J. 106:571, 1983.
19. MacMahon, S. W., Roberts, J. K., Kramer-Fox, R., Zucker, D. M., Roberts, R. B., and Devereux, R. B.: Mitral valve prolapse and infective endocarditis. Am. Heart J. 113:1291, 1987.
20. Dajani, A. S., Bisno, A. L., Chung, K. J., Durack, D. T., Freed, M., Gerber, M. A., Karchmer, A. W., Millard, H. D., Rahimtoola, S., Shulman, S. T., Watanakunakorn, C., and Taubert, K. A.: Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 264:2919, 1990.
21. Rosenblum, M. L., Mampalam, T. J., and Pons, V. G.: Controversies in the management of brain abscesses. Clin. Neurosurg. 33:603, 1986.
22. Haimes, A. B., Zimmerman, R. D., Morgello, S., Weingarten, K., Becker, R. D., Jennis, R., and Deck, M. D. F.: MR imaging of brain abscesses. Am. J. Roentgenol. 152:1073, 1989.
23. Berg, B., Franklin, G., Cuneo, R., Boldrey, E., and Strimling, B.: Nonsurgical cure of brain abscess. Early diagnosis and follow-up with computerized tomography. Ann. Neurol. 3:474, 1978.
24. Rosenblum, M. L., Hoff, J. T., Norman, D., Edwards, M. S., and Berg, B. O.: Nonoperative treatment of brain abscesses in selected high-risk patients. J. Neurosurg. 52:217, 1980.

OPHTHALMIC MINIATURE

His pupils enlarge as he leans closer to the mirror, making a shadow, seeking to see if there truly is a soul. That's what he used to think ophthalmologists were looking at when they pressed that little hot periscope of a flashlight tight against your eye. What they saw, they never told him. He sees nothing but black, out of focus, because his eyes are aging.

John Updike, *Rabbit, Run*
New York, Alfred A. Knopf, 1981, p. 303

Management of Endophthalmitis While Preserving the Uninvolved Crystalline Lens

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Twelve phakic eyes (11 patients) with culture-positive endophthalmitis were treated without removal of the uninvolved crystalline lens. Eight eyes were treated by pars plana vitrectomy and intraocular injection of antibiotics. Four eyes were treated with intraocular antibiotic injection alone. The clinical infection was successfully eradicated in all patients, including one patient treated with reinjection of antibiotics. During follow-up after successful treatment, eight eyes had progression of a preexisting lens opacification, two eyes had stable lens opacification, and two eyes maintained clear lenses. Six of 12 eyes achieved 20/80 or better visual acuity with an average follow-up time of 13 months. Six of eight eyes treated with pars plana vitrectomy and intraocular antibiotic injection achieved this level of visual acuity in contrast to none of four eyes treated with only intraocular antibiotic injection. These results indicated that endophthalmitis in phakic eyes can be successfully treated while preserving a clear, uninvolved crystalline lens by the use of pars plana vitrectomy and intraocular administration of appropriate antibiotics.

ALTHOUGH ENDOPHTHALMITIS develops most commonly after a cataract operation, endophthalmitis may also develop in phakic eyes.[1-4] Because of the various presentations of endophthalmitis in phakic eyes, a review of the literature is not conclusive as to the management of an uninvolved crystalline lens in such cases. Removal of the crystalline lens at the time of vitrectomy is often considered to avoid future cataract formation or to aid in the clearance of the infection.[1] Fully developed cataracts (for example, after penetrating trauma) are usually removed to enable visualization during the pars plana vitrectomy. Lenses directly involved in the infectious process are generally removed to treat the infection adequately.[5]

To address this issue, we reviewed the course of infection in 12 eyes with endophthalmitis in which the uninvolved crystalline lens was preserved. The long-term follow-up of these cases, including the status of the crystalline lens, was studied.

Patients and Methods

The medical records of all patients with culture-proven endophthalmitis examined between January 1980 and December 1990 at the Bascom Palmer Eye Institute were reviewed. Of 392 identified cases, 23 cases of endophthalmitis (24 eyes) were observed in which the crystalline lens was present preoperatively. Ten eyes in nine patients were identified in which the uninvolved crystalline lens was retained during treatment for endophthalmitis. Two cases (Cases 3 and 7) involving patients treated at the Geisinger Medical Center in 1989 were similar and were added to our study. The lenses were uninvolved and preserved in these 12 eyes (11 patients) with endophthalmitis that composed our study population. The lens was removed in conjunction with primary endophthalmitis treatment in eight of the 14 eyes that did not remain phakic after treatment at Bascom Palmer Eye Institute, and six eyes were enucleated. The causes for lens extraction were multifactorial but in most cases, direct lens involvement in the traumatic or infectious process, or both, was the reason for removal.

The 11 patients ranged in age from 14 to 81 years and included seven males and four fe-

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TABLE 1
CHARACTERISTICS OF PATIENTS WITH ENDOPHTHALMITIS AND PREDISPOSING FACTORS*

PATIENT NO., AGE (YRS), GENDER, EYE	CATEGORY	PREDISPOSING FACTOR
1, 79, F, R.E.	Endogenous	Intensive systemic antibiotic therapy after a bowel operation
2, 51, M, R.E.	Endogenous	Cirrhosis, chronic dermatitis, foot ulcer
3, 66, F, R.E.	Endogenous	Diabetes mellitus, systemic candidiasis
4, 22, F, R.E.	Endogenous	Long-term systemic antibiotic therapy for extensive thermal burn
5, 62, F, R.E.	Endogenous	Small-bowel resection
6, 81, M, both eyes	Endogenous	Bacterial endocarditis
7, 27, M, L.E.	Trauma	Steel-wire in-and-out perforation
8, 47, M, R.E.	Postoperative	Status post radial keratotomy
9, 68, M, R.E.	Postoperative	Status post removal of infected scleral buckle
10, 80, M, L.E.	Postoperative	Status post glaucoma-filtering surgery
11, 14, M, L.E.	Postoperative	Status post glaucoma-filtering surgery

*Cases 1, 2, and 4 through 6 were previously reported,[4] and Case 8 was previously reported.[2]

males. The right eye was involved in seven patients, the left eye was involved in three patients, and both eyes were involved in one patient. The cause of endophthalmitis was endogenous in six patients, posttraumatic in one patient, and postoperative in four patients (Table 1). Seven eyes were treated initially with pars plana vitrectomy with intraocular injection of antibiotics and five eyes were treated with intraocular antibiotics alone after vitreous aspiration for culturing. Because of a presumed fungal origin, the patients with endogenous endophthalmitis were treated with amphotericin B (5 μg) with or without systemic antifungal therapy. Generally, patients with presumed bacterial endophthalmitis were treated with gentamicin (0.1 mg) or vancomycin (1.0 mg), or both, after 1986. In the patients treated before 1987, cefazolin (2.25 mg) was used instead of vancomycin. A patient with filtering-bleb–associated endophthalmitis was treated initially with intraocular injection of antibiotics alone (Case 9) and then was treated with a second intraocular injection of antibiotics because of suspected recurrence (Table 2).

Candida albicans was cultured in five of the six patients with endogenous endophthalmitis. *Streptococcus* species were identified in three patients, including one patient with mixed fungal and bacterial infection (Case 4). The remaining patients had endophthalmitis caused by *Staphylococcus aureus* (one), *S. epidermidis* (one), *Pseudomonas stutzeri* (one), and *Haemophilus influenzae* (one; Table 2). The preoperative visual acuities were poor and ranged from 20/200 to light perception (Table 3). The choice between treatment with pars plana vitrectomy or medical treatment alone was determined by individual physician preference in this study.

Results

Six of seven patients achieved 20/80 or better visual acuity after treatment with pars plana vitrectomy and intravitreal administration of antibiotics (Cases 1 through 4, 7, and 8; Table 3). Three of these six eyes (Cases 3, 4, and 7) had no observable progression of cataract after follow-up times ranging from one to 15 months. The patient in Case 1 developed progressive nuclear sclerosis after vitrectomy but retained 20/30 +2 visual acuity after 48 months of follow-up. The patient in Case 8 achieved a visual acuity of 20/30 two months after treatment, but developed a progressive nuclear sclerotic cataract 29 months postoperatively, thereby reducing the visual acuity to 20/300. This patient underwent a successful cataract operation with a return of 20/25 visual acuity six months after removal of the cataract. The patient in Case 2 regained 20/30 visual acuity and had mild progression of preexisting nuclear sclerosis. The patient in Case 5 underwent pars plana vitrectomy with intraocular injection of amphotericin B. The clear lens was

TABLE 2

CLINICAL FEATURES, SURGICAL MANAGEMENT, AND CULTURE RESULTS OF ENDOPHTHALMITIS IN 11 PATIENTS

PATIENT NO.	ANTERIOR CHAMBER REACTION	LENS STATUS	VITREITIS	CHORIO-RETINITIS	TREATMENT/INTRAOCULAR THERAPY	CULTURE RESULT
1	2+ cell	1+ nuclear sclerosis	1+/1+	Present	Vitrectomy/ amphotericin	*Candida albicans*
2	1+ cell	Trace nuclear sclerosis	3+	Absent	Vitrectomy/ amphotericin	*C. albicans*
3	1+ cell	2+ nuclear sclerosis	3+	Present	Vitrectomy/ amphotericin/ dexamethasone	*C. albicans*
4	2+ cell	Clear	3+	Absent	Vitrectomy/ amphotericin/ vancomycin	*C. albicans, Streptococcus* viridans*
5	Trace cell	Clear	3+	Absent	Vitrectomy/ amphotericin	*C. albicans*
6, R.E.	Trace cell	3+ nuclear sclerosis	4+	Not recorded	Vitreous aspiration/ vancomycin	*Streptococcus bovis*
6, L.E.	Trace cell	3+ nuclear sclerosis	4+	Not recorded	Vitreous aspiration/ vancomycin	*St. bovis*
7	Hypopyon	Clear	4+	Not recorded	Vitrectomy/ gentamicin/ cefazolin	*Pseudomonas stutzeri*
8	Hypopyon	Clear	4+	Not recorded	Vitrectomy/ gentamicin/ cefazolin	*Staphylococcus epidermidis*
9	2+ cell	2+ nuclear sclerosis/ 1+ posterior subcapsular opacity	2+	Absent	Vitreous aspiration/ gentamicin/ cefazolin†	*S. aureus*
10	Hypopyon	2+ nuclear sclerosis	3+	Absent	Anterior chamber and vitreous aspiration/ gentamicin/ cefazolin	*Streptococcus* sp.
11	Hypopyon	3+ nuclear sclerosis/ 3+ posterior subcapsular opacity	3+	Absent	Anterior chamber and vitreous aspiration/ gentamicin/ cefazolin	*Haemophilus influenzae*

*Mixed infection.

†Injection at one week for suspected recurrent infection.

preserved. Postoperatively, a 360-degree choroidal detachment with hypotony developed. Total retinal detachment and progressive posterior subcapsular cataract developed three weeks after the operation, although persistent infection was not evident. Pars plana vitrectomy, lensectomy, membrane peeling, fluid-gas exchange, and endophotocoagulation reattached the retina on the first retinal reattachment procedure, but recurrent retinal detachment occurred. The patient refused further surgical treatment.

Four of five eyes treated with intraocular antibiotic injection alone had a poor posttreatment visual outcome (Cases 6, 10, and 11). Three of these four eyes developed chronic hypotony and phthisis bulbi. The patient in Case 9 had only mild progression of a preexist-

TABLE 3
VISUAL RESULTS AND FINAL LENS STATUS

PATIENT NO.	PRETREATMENT VISUAL ACUITY	FINAL VISUAL ACUITY	FINAL LENS STATUS	FOLLOW-UP (MOS)	COMMENT
1	2/200	20/25−3	2+ nuclear sclerosis	46	Inactive chorioretinal scar
2	8/200	20/30	1+ nuclear sclerosis	6	Deceased
3	1/200	20/60	2+ nuclear sclerosis	15	Diabetic macular edema
4	20/200	20/80	Clear	0.75	Macular epiretinal membrane
5	1/200	No light perception	4+ posterior subcapsular opacity	3.5	Recurrent retinal detachment
6, R.E.	Light perception	1/200	3+ nuclear sclerosis 2+ posterior subcapsular opacity	15	Visual acuity 20/400 6 months after cataract operation
6, L.E.	Light perception	No light perception	Not recorded	15	Phthisis bulbi
7	Light perception	20/25+2	Clear	6	No anterior chamber or vitreous cells
8	1/200	20/25	3+ nuclear sclerosis	35	Cataract operation, preoperative visual acuity 20/300 29 months after vitrectomy
9	Hand motions	Hand motions	3+ nuclear sclerosis 1+ posterior subcapsular opacity	0.75	Did not return for follow-up
10	8/200	Light perception	2+ nuclear sclerosis	0.75	Chronic hypotony
11	20/400	Light perception	1+ nuclear sclerosis 3+ posterior subcapsular opacity	3.5	Chronic hypotony

ing cataract three weeks after culture and injection of antibiotics, but was lost to follow-up. The patient in Case 6 developed bilateral endogenous *Streptococcus bovis* endophthalmitis as a complication of acute bacterial endocarditis. Initial visual acuity was light perception in both eyes. Vancomycin (0.1 mg) was injected intraocularly into both eyes at the time of vitreous aspiration for culturing. The visual acuity decreased to no light perception in the left eye because of angle-closure glaucoma. The patient underwent cataract extraction with intraocular lens implantation for progressive lens opacification after successful treatment in the right eye. The best-corrected visual acuity after cataract extraction was 20/400 after 15 months of follow-up.

Case Reports

Case 1

A 79-year-old woman underwent repair of a bowel perforation that complicated routine colonoscopy in May 1987. During the hospitalization she was treated with multiple intravenously administered antibiotics.

The patient was admitted to the Ophthalmology Service in June 1987 with a 16-day history of decreased visual acuity, floaters, and gradually increasing pain in the right eye. The visual acuity was 20/200 in both eyes (the left eye was amblyopic). Slit-lamp examination of the right eye disclosed mild conjunctival injection with clear cornea and mild anterior chamber reaction. She had mild nuclear sclerosis of the lens. A posterior segment examination disclosed diffuse vitreous cellular infiltrates. A 1- to 2-disk-diameter white retinal infiltrate was observed inferior to the optic disk and was considered to be consistent with an area of active chorioretinitis. Five days after initial examination, the patient's visual acuity decreased to 2/200 in the right eye. The vitreous infiltrates progressed and presumed fungal endophthalmitis was diagnosed. One day later, a pars plana vitrectomy and intraocular injection of amphotericin B (5 μg) were performed. Cultures of the vitreous were positive for *C. albicans*, although blood cultures remained negative. The patient was treated with oral administration of 200 mg of ketoconazole twice daily for two weeks. The visual acuity was 20/200 at the time of hospital discharge seven days after the vitrectomy. On follow-up examination, the previous area of chorioretinitis had only a small atrophic chorioretinal scar. The visual acuity 48 months after vitrectomy was 20/30 +2 with moderate nuclear sclerosis of the lens.

Case 2

A 51-year-old man with a history of alcoholic cirrhosis, chronic ulcers on both feet, chronic obstructive pulmonary disease, and chronic atopic dermatitis was admitted to the Ophthalmology Service in December 1985 because of a two-month history of progressive visual loss in the right eye. Initial examination disclosed a visual acuity of 20/50 and moderate vitreitis in the right eye. The lens had mild nuclear sclerosis. Over the next few days, the visual acuity decreased to 8/200, and organized cellular infiltrates were more prominent in the vitreous cavity. Fungal endophthalmitis was clinically diagnosed. Five days after initial examination, the patient underwent an uncomplicated pars plana vitrectomy with intraocular injection of amphotericin B (5 μg) in the right eye. Vitreous cultures were positive for *C. albicans*. The patient was also treated with oral administration of 200 mg of ketoconazole for three weeks. The final visual acuity was 20/30 after six months of follow-up with slight progression of his preexisting nuclear sclerotic cataract.

Case 8

A 47-year-old man underwent a 16-incision radial keratotomy in the right eye in December 1981. A corneal perforation occurred during the operation. Nine days postoperatively, the patient had marked anterior chamber reaction and a 5% hypopyon. The lens was clear at the time of initial examination. A marked cellular reaction was observed in the vitreous cavity, which contained fluffy white opacities. The visual acuity decreased to counting fingers at 1 foot. The retina was attached but was poorly seen because of the vitreous reaction.

The patient underwent a pars plana vitrectomy and anterior chamber paracentesis for presumed bacterial endophthalmitis. At the conclusion of the surgical procedure, gentamicin (0.1 mg) and cefazolin (2.2 mg) were injected intraocularly. Gentamicin (40 mg) and cefazolin (100 mg) were also injected periocularly. The patient was not treated with periocularly administered corticosteroids.

Staphylococcus epidermidis was isolated from both the aqueous and vitreous specimens. The isolate was sensitive to gentamicin and cefazolin. The patient was treated with intravenously administered gentamicin (70 mg, every eight hours) and cefazolin (1 g, every six hours) for six days as well as gentamicin eyedrops (9.1 mg/dl every hour), cefazolin eyedrops (50 mg/dl every hour), and topically applied prednisolone acetate (1%, every two hours).

On discharge, the intraocular inflammation had improved and the visual acuity was counting fingers at 1 foot. Ten months postoperatively, the visual acuity was 20/60 and anterior chamber reaction was minimal. At one year follow-up, the best-corrected visual acuity was 20/30 −2. The lens had remained clear, and the vitreous cavity had minimal cellular debris. A progressive nuclear sclerotic cataract subsequently developed with gradual visual acuity loss to 20/300. An extracapsular cataract extraction with posterior chamber intraocular lens implantation was performed in 1985. The final visual acuity was 20/25 six months after the cataract extraction. The initial treatment results in this case were reported in 1982.[2]

Discussion

Little information regarding the management of the uninvolved crystalline lens in eyes with endophthalmitis is published. In addition to a vitrectomy, pars plana lensectomy offers the theoretical advantage of more complete removal of infective organisms in eyes with advanced endophthalmitis or anterior segment opacities. When intraocular infection is less severe, lensectomy may not be necessary in eyes with clear uninvolved lenses. We undertook this study to determine the course of disease of phakic eyes treated for endophthalmitis with preservation of the crystalline lens after treatment.

In our series of patients, we did not observe immediate postoperative cataract in any patient, although transient feathering of the posterior lens capsule was present in many patients. Although our overall follow-up time was short, four of our patients did not develop progressive cataract. Two patients (Cases 4 and 7) maintained a clear crystalline lens (after three weeks and six months of follow-up, respectively). These two patients were both younger than 30 years of age. In a study of phakic diabetic patients undergoing pars plana vitrectomy, Novak and associates[6] reported that the development of nuclear sclerosis was associated with increasing patient age and that posterior subcapsular opacification was associated with increased operating time and use of a large intravitreal gas bubble.

In 1984, Michels[7] reported a 34% incidence of nuclear sclerotic cataract one year after vitrectomy for macular pucker. Two more recent reports from the same institution evaluated cataract progression after vitrectomy. DeBustros and associates[8] stated that the cumulative risk for development of a nuclear sclerotic cataract after vitrectomy and epiretinal membrane removal was 31% at one year and 72% at two years. In their study published in 1991 that evaluated progression of nuclear sclerosis after vitrectomy for idiopathic epiretinal membranes, 80% of the operated-on eyes (vs 24% of the fellow eyes) were found to have visually significant nuclear sclerosis on follow-up. Additionally, the concentration of glucose in the infusion fluid was not associated with cataract formation in these patients without diabetes, and patients older than 50 years of age had a greater rate of progressive nuclear sclerosis.[9]

The long-term effect of intravitreal administration of antibiotics on cataractogenesis has not been established. However, higher than recommended doses of aminoglycosides or amphotericin B have been shown to cause the rapid development of a cataract in animal models.[10-12] Intraocular, topical, and periocular administration of corticosteroids are well-known causes of posterior subcapsular cataract formation.[13,14] The interaction between corticosteroid and antibiotic therapy in the pathogenesis of cataract formation in the severely inflamed eye is not known.

Other theoretical causes for cataract formation after endophthalmitis and its treatment include the effect of toxins and inflammatory end products from an infectious process as well as the potential role of the intraocular infusion solution on lens metabolism and capsule permeability.[9,15,16] Light from the operating microscope or reflected light from the endoilluminator may also have a role in cataract formation,[17] although this has not yet been proven.

Because most of our patients developed slowly progressive cataract formation after their endophthalmitis treatment, preserving the crystalline lens may allow conventional cataract extraction with posterior chamber intraocular lens implantation at a later date. Placing an intraocular lens into an eye with an active infection is not generally recommended. An exception to this general rule occurs in the case of delayed-onset pseudophakic endophthalmitis caused by *Propionibacterium acnes* in which intraocular lens removal, removal of the capsular bag, and secondary intraocular lens implantation may be considered.[18] Another potential advantage of leaving the crystalline lens within the eye is the increased half-life of intraocularly injected antibiotics in phakic eyes compared to the half-lives of antibiotics in pseudophakic or aphakic eyes. This increased half-life of the drugs may reduce the need for repeat intraocular injection of antibiotics.[19-21]

Although the number of cases in our study was too small to reach statistical significance, our results indicated that pars plana vitrectomy with intraocular injection of antibiotics is an effective treatment for endophthalmitis in eyes with an uninvolved crystalline lens. Our patients treated by vitrectomy had better visual outcome compared to that of patients treated with vitreous aspiration and intraocular injection of antibiotics alone. However, patients treated with vitrectomy generally had more benign infections (caused by *C. albicans*, five patients; and *S. epidermidis*, one patient) compared to the five patients not treated with vitrectomy whose infections were caused by more virulent bacteria. On the basis of our experience in this study of phakic eyes, we do not recommend the removal of an uninvolved crystalline lens unless marked anterior segment inflammation or preexisting cataract obscures the view for pars plana vitrectomy.

References

1. Greenwald, M. J., Wohl, L. G., and Sell, C. H.: Metastatic bacterial endophthalmitis. A contemporary reappraisal. Surv. Ophthalmol. 31:81, 1986.
2. Gelender, H., Flynn, H. W., Jr., and Mandelbaum, S. H.: Bacterial endophthalmitis resulting from radial keratotomy. Am. J. Ophthalmol. 93:323, 1982.
3. Mandelbaum, S., and Forster, R. K.: Endophthalmitis associated with filtering blebs. Int. Ophthalmol. Clin. 27:107, 1987.
4. Brod, R. D., Flynn, H. W., Jr., Clarkson, J. G., Pflugfelder, S. C., Culbertson, W. W., and Miller, D. A.: Endogenous *Candida* endophthalmitis. Management without intravenous amphotericin B. Ophthalmology 97:666, 1990.
5. Clinch, T. E., Duker, J. S., Eagle, R. C., Jr., Calhoun, J. H., Augsburger, J. J., and Fischer, D. H.: Infantile endogenous *Candida* endophthalmitis presenting as a cataract. Surv. Ophthalmol. 34:107, 1989.
6. Novak, M. A., Rice, T. A., Michels, R. G., and Auer, C.: The crystalline lens after vitrectomy for diabetic retinopathy. Ophthalmology 91:1480, 1984.
7. Michels, R. G.: Vitrectomy for macular pucker. Ophthalmology 91:1384, 1984.
8. deBustros, S., Thompson, J. T., Michels, R. G., Enger, C., Rice, T. A., and Glaser, B. M.: Nuclear sclerosis after vitrectomy for idiopathic epiretinal membranes. Am. J. Ophthalmol. 105:160, 1988.
9. Cherfan, G. M., Michels, R. G., deBustros, S., Enger, C., and Glaser, B. M.: Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker. Am. J. Ophthalmol. 111:434, 1991.
10. Bennett, T. O., and Peyman, G. A.: Toxicity of intravitreal aminoglycosides in primates. Can. J. Ophthalmol. 9:475, 1974.
11. Kattan, H., and Pflugfelder, S. C.: Complications of intraocular antimicrobial agents. Int. Ophthalmol. Clin. 29:188, 1989.
12. Souri, E. N., and Green, W. R.: Intravitreal amphotericin B toxicity. Am. J. Ophthalmol. 78:77, 1974.
13. Spaeth, G. L., and von Sallmann, L.: Corticosteroids and cataracts. Int. Ophthalmol. Clin. 6:915, 1966.
14. Urban, R. C., and Cotlier, E.: Corticosteroid-induced cataracts. Surv. Ophthalmol. 31:102, 1986.
15. Glasser, D. B., and Edelhauser, H. F.: Toxicity of surgical solution. Int. Ophthalmol. Clin. 29:179, 1989.
16. Bloemendal, H.: Disorganization of membranes and abnormal intermediate filament assembly lead to cataract. Invest. Ophthalmol. Vis. Sci. 32:445, 1991.
17. Borkman, R. F., and Lerman, S.: Evidence for free radical mechanism in aging and UV irradiated ocular lenses. Exp. Eye. Res. 25:203, 1977.
18. Fox, G. M., Joondeph, B. C., Flynn, H. W., Jr., Pflugfelder, S. C., and Roussel, T. J.: Delayed-onset pseudophakic endophthalmitis. Am. J. Ophthalmol. 111:163, 1991.
19. Barza, M.: Antibacterial agents in the treatment of ocular infections. Infect. Dis. Clin. North Am. 3:533, 1989.
20. Ficker, L., Meredith, T. A., Gardner, S., and Wilson, L. A.: Cefazolin levels after intravitreal injection. Effects of inflammation and surgery. Invest. Ophthalmol. Vis. Sci. 31:502, 1990.
21. Doft, B. H., Weiskopf, J., Nilsson-Ehle, I., and Wingard, L. B., Jr.: Amphotericin clearance in vitrectomized versus nonvitrectomized eyes. Ophthalmology 92:1601, 1985.

OPHTHALMIC MINIATURE

Her memories of the medicine show in Medora had begun to fill out. "He stuck something that was supposed to be a third eye in the middle of his forehead and claimed to be from Egypt or somewhere. Anybody could see that the third eye was just made of glass. But I guess it fooled some of the cowboys—the drunk ones at least. He pretended he could see the future and charged fifty cents for fortunes."

Larry McMurtry, *Buffalo Girls*
New York, Simon and Schuster, 1990, p. 57

Medial Rectus Muscle Marginal Myotomies for Persistent Esotropia

Jan-Tjeerd H. N. de Faber, M.D., and Gunter K. von Noorden, M.D.

We reviewed the records of 18 patients with persistent esotropia after maximal recession of each medial rectus muscle on whom marginal myotomy of both medial recti muscles was subsequently performed. We compared the results in patients with essential infantile esotropia, acquired esotropia, nonaccommodative convergence excess, and nystagmus compensation syndrome. After a follow-up of three years, the mean improvement of esotropia at distance fixation was 9 prism diopters (range, −20 to +41 prism diopters) and was 21 prism diopters at near fixation (range, +4 to +50 prism diopters). The effect of marginal myotomy of previously maximally recessed medial recti muscles is unpredictable. However, we believe it to be an acceptable secondary surgical procedure in selected cases of persistent esotropia. The best results were obtained in essential infantile esotropia.

MARGINAL MYOTOMY is a surgical technique in which one or more incisions are made in the margins of an extraocular muscle to lengthen it and thus to decrease its function. As early as 1857, von Graefe reported marginal myotomy as a treatment of strabismus.[1] Many variations of this technique have been proposed subsequently.[2,3]

Marginal myotomy is no longer an accepted primary procedure for esotropia because the current technique of measured, reversible recession is a more predictable method of weakening the action of a previously unoperated-on extraocular muscle.[4] Marginal myotomy, however, may be indicated as a secondary or tertiary procedure when an esotropia persists despite a previous maximal operation on all four horizontal muscles. The purpose of this study was to determine the long-term effect of marginal myotomies of the medial recti muscles in patients with persistent esotropia after an operation for essential infantile esotropia, acquired esotropia, nonaccommodative convergence excess,[5] and nystagmus compensation syndrome esotropia.[6]

Subjects and Methods

The charts of all patients with esotropia who underwent marginal myotomy by one of us (G.K.v.N.) between 1972 and 1986 at the Texas Children's Hospital were reviewed. Patients who satisfied the following criteria were included: (1) an 80% double marginal myotomy of both medial recti muscles was the only surgical treatment, (2) postoperative measurements were performed six weeks and three years after the operation, and (3) no other ocular or neurologic disease was observed. Eighteen patients met these criteria. Each had undergone a previous operation for esotropia that consisted of maximal recession (5 to 8 mm) of both medial recti muscles. In 12 patients this was combined with or succeeded by myectomy of both inferior oblique muscles, resection (5 to 9 mm) of one or both lateral recti muscles or retroequatorial myopexy of the medial recti muscles (Table).

The 18 patients were divided into the following four groups: (1) essential infantile esotropia, (2) acquired esotropia, (3) nonaccommodative convergence excess, and (4) nystagmus compensation syndrome (Table). The mean age at the time of the operation was 9.4 years with a

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TABLE
PRE- AND POSTOPERATIVE MEASUREMENT OF ESOTROPIA IN PRISM DIOPTERS

CASE NO., AGE AT TIME OF OPERATION (YRS)	DIAGNOSIS	NEAR FIXATION			DISTANCE FIXATION			PREVIOUS OPERATIONS IN ADDITION TO MAXIMAL RECESSION OF MEDIAL RECTUS MUSCLE IN BOTH EYES
			POSTOPERATIVE			POSTOPERATIVE		
		PREOPERATIVE	6 WKS	3 YRS	PREOPERATIVE	6 WKS	3 YRS	
1, 1.5	Infantile esotropia	45	18	12	—	—	—	Resection of lateral rectus muscle, both eyes
2, 12		40	2	−18	35	9	−6	Resection of lateral rectus muscle, both eyes; myectomy of inferior oblique muscle, L.E.
3, 10		30	12	3	14	2	−10	—
4, 12		30	12	6	16	2	5	Resection of lateral rectus muscle, both eyes; myectomy of inferior oblique muscle, L.E.
5, 2		25	20	14	25	10	−10	Resection of lateral rectus muscle, both eyes; myectomy of inferior oblique muscle, both eyes
6, 4		20	16	16	12	7	14	Resection of lateral rectus muscle, both eyes
7, 10		16	8	7	2	2	6	Recession resection procedure, R.E.; resection of lateral rectus muscle, both eyes; myectomy of inferior oblique muscle, both eyes
8, 10	Acquired esotropia	50	20	25	40	5	20	—
9, 3.5		30	18	25	8	5	17	Myectomy of inferior oblique muscle, R.E.
10, 14		18	4	2	5	2	4	—
11, 11	Nonaccommodative convergence excess	40	8	12	20	9	4	—
12, 5		35	16	30	10	−14	20	—
13, 10		25	−16	−10	12	−25	−20	—
14, 11		25	14	20	2	3	8	Retroequatorial myopexy of medial rectus muscle, both eyes
15, 7	Nystagmus compensation syndrome	47	−7	2	10	−25	−4	Resection of lateral rectus muscle, both eyes; retroequatorial myopexy of medial rectus muscle, both eyes
16, 9		33	2	−2	25	7	7	Resection of lateral rectus muscle, both eyes; retroequatorial myopexy of medial rectus muscle, both eyes
17, 4		30	14	20	2	2	22	Resection of lateral rectus muscle, both eyes; retroequatorial myopexy of medial rectus muscle, both eyes
18, 14		25	9	14	14	10	8	Myectomy of inferior oblique muscle, both eyes

range of 1.5 to 14 years. The preoperative and postoperative deviations were measured at near and distance fixation with the prism and cover test with the patient's refractive error fully corrected.

The surgical indications for marginal myotomy of both medial recti muscles were the following: (1) persistent convergence excess esotropia at near but not at distance fixation after maximal (5 to 8 mm) recession of both medial recti muscles, or (2) a residual esotropia at near and distance fixation after repeated and maximal operations of the four horizontal recti muscles.[7] Our first choice in these types of deviation is retroequatorial myopexy of the medial recti muscles, after verifying that the medial recti muscles have been maximally recessed.[8] We prefer this procedure to marginal myotomies because the myopexy may be reversed. When exposure is difficult or there is extensive scarring from a previous operation, marginal myotomy of the medial recti muscles remains the only alternative to obtain additional correction.

Our technique is similar to that of von Blaskovics and Kreiker[3] and Helveston and Cofield.[4] The medial rectus muscle is exposed and incised using thermocautery perpendicular to its superior edge, approximately 5 mm behind its insertion. The second incision is from the inferior edge of the muscle, 3 mm from the insertion. About 80% of the muscle fibers are sectioned with each incision. The posterior myotomy is performed first to facilitate exposure. The double marginal myotomy results in a Z configuration, which lengthens the muscle while retaining its arc of contact to the sclera.

Results

The preoperative angle of esotropia was compared with the postoperative measurements six weeks and three years after the operation at near fixation (Figure, top) and at distance fixation (Figure, bottom). The mean improvement of esotropia three years after the bimedial marginal myotomy was 21 prism diopters at near

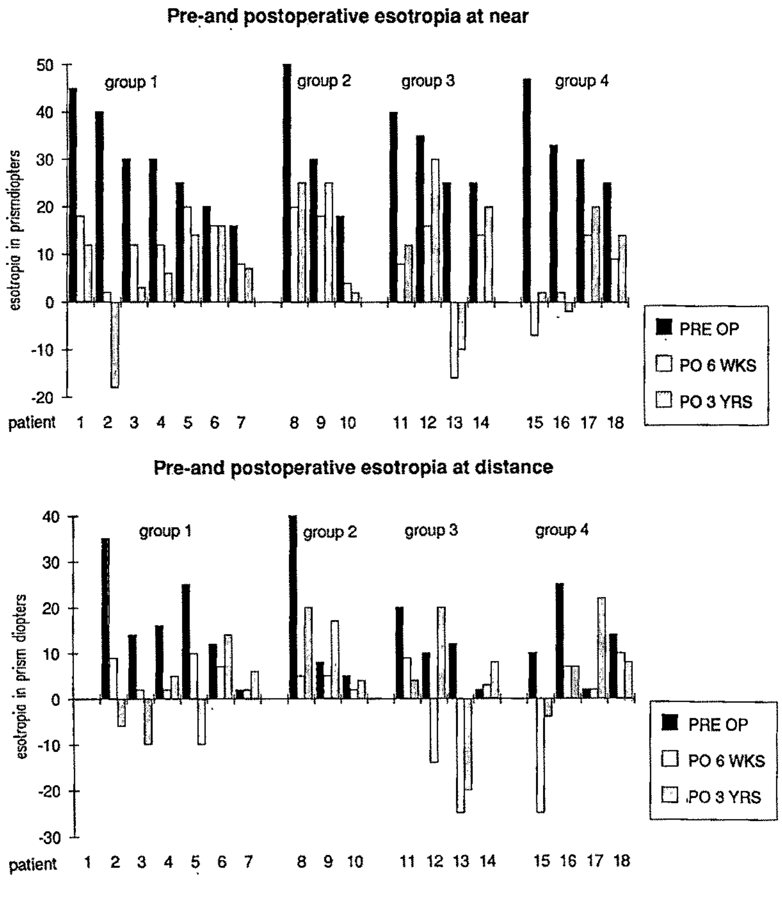

Figure (de Faber and von Noorden). Histograms of the pre- and postoperative esotropia in prism diopters at near fixation (top) and at distance fixation (bottom). Group 1 is essential infantile esotropia, Group 2 is acquired esotropia, Group 3 is nonaccommodative convergence excess, and Group 4 represents the measurements of patients with nystagmus compensation-type esotropia. PRE OP indicates preoperative, PO indicates postoperative. Numbers 1 through 18 on the x-axis correspond with the case numbers in the Table.

fixation (range, 4 to 58 prism diopters) and 9 prism diopters at distance fixation (range, −20 to +41 prism diopters). The sample was too small for statistical analysis. The range of postoperative improvement of esotropia indicated the effect of marginal myotomy to be unpredictable. The reduction of esotropia at near fixation was greater than that at distance fixation. Esotropia was not recurrent in the essential infantile esotropia group, and was less severe in six of seven patients three years after the operation as compared to the measurements six weeks after the operation. In other patients the results were less permanent. The esotropia was greater three years after the operation than it was after six weeks in nine of 11 patients. None of the 18 patients had a functionally marked limitation of adduction.

Discussion

Marginal myotomy of the medial recti muscles was used in these patients as a last resort to correct persistent esotropia. The procedure was more effective at near fixation than it was at distance fixation and the most permanent results were obtained in essential infantile esotropia.

With the exception of the anecdotal observation by von Blaskovics and Kreiker,[3] who mentioned a 10- to 16-prism diopter effect from bimedial marginal myotomies, no other information exists in the literature regarding the quantitative effect of isolated marginal myotomies of both medial recti muscles in persistent esotropia.[9-12]

The most feared complication of a marginal myotomy is an unintentional 100% myotomy, with subsequent loss of the muscle. This did not occur in our study. Marginal myotomy, however, is a crippling procedure, as it reduces irreversibly the number of contractile elements. Also, because of extensive scarring, reoperation of a muscle that has undergone myotomy becomes virtually impossible. An overcorrection after marginal myotomy is an undesirable complication. It occurred in one patient in our study (Case 13) who required additional recession of both lateral recti muscles to correct the consecutive exotropia.

References

1. von Graefe, A.: Beitraege zur Lehre vom Schielen und von der Schiel-Operation. Arch. Ophthalmol. 3:177, 1857.
2. Duke-Elder, S.: Anomalies of Ocular Motility. In System of Ophthalmology, vol. 6. St. Louis, C. V. Mosby Co., 1973, p. 498.
3. von Blaskovics, L., and Kreiker, A.: Eingriffe am Auge. Stuttgart, Ferdinand Enke Verlag, 1945, p. 396.
4. Helveston, E. M., and Cofield, D. D.: Indications for marginal myotomy and technique. Am. J. Ophthalmol. 70:574, 1970.
5. von Noorden, G. K., and Avilla, C. W.: Nonaccommodative convergence excess. Am. J. Ophthalmol. 101:70, 1986.
6. von Noorden, G. K.: Binocular vision and ocular motility. Theory and management of strabismus, ed. 4. St. Louis, C. V. Mosby Co., 1990, p. 438.
7. von Noorden, G. K., and Munoz, M.: Recurrent esotropia. J. Pediatr. Ophthalmol. Strabismus 88:275, 1988.
8. von Noorden, G. K.: An alternative to marginal myotomy. Am. J. Ophthalmol. 94:285, 1982.
9. McPhee, T. J., Dyer, J. A., and Ilstrup, D. M.: Marginal myotomy of the medial rectus with lateral rectus resection as a secondary procedure for esotropia. Graefes Arch. Clin. Exp. Ophthalmol. 226:197, 1988.
10. Morgan, A. L., and Arstikaitis, M. J.: Postoperative report on 200 cases of marginal myotomies. Trans. Can. Ophthalmol. Soc. 9:129, 1957.
11. Gibson, G. G.: Bilateral marginal myotomy. Trans. Am. Ophthalmol. Soc. 56:791, 1952.
12. Zak, T. A., and Morin, J. D.: Surgery of infantile esotropia. A critical evaluation of marginal myotomy of the medial recti as a primary and secondary procedure. J. Pediatr. Ophthalmol. Strabismus 20:52, 1983.

Diameter of Normal Extraocular Recti Muscles With Echography

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To establish the range of diameters of normal extraocular muscles, we used standardized A-scan echography to measure the superior recti/levator complex, medial, lateral, and inferior recti muscles in 38 subjects with healthy orbital tissues. The relationships of age, gender, height, and weight to axial length of the globe were considered. These factors and extraocular muscle diameters were not consistently associated. Our normative data were compared with previously reported studies of extraocular muscle diameter performed with standardized A-scan and contact B-scan echography and computed tomographic scanning.

THE DIAMETER of the extraocular muscles may be of diagnostic importance in patients with diplopia, both with and without typical clinical signs or symptoms of orbital disease. The accurate assessment of extraocular muscle size is, therefore, of vital clinical importance in the proper management and examination of individuals with orbital vs neuro-ophthalmologic disorders.[1]

Computed tomography, magnetic resonance imaging, and echography are techniques used to image the extraocular muscles and other orbital structures. Sometimes, standardized echography (contact B-scan and standardized A-scan) is used initially to screen the orbital tissues to detect and characterize extraocular muscle thickening or other pathologic changes. The echographic findings are then considered, in conjunction with the clinical examination, to determine which (if any) investigations are further warranted.

Ossoinig[2,3] was the first to describe examination techniques using standardized A-scan instrumentation for examining the extraocular recti muscles. In 1977, McNutt, Kaefring, and Ossoinig[4] first reported values for normal extraocular rectus muscle diameter as measured with standardized A-scan. Since that time, remarkable technical improvements have been made in both ultrasound instrumentation and in examination techniques. In accordance with these improvements, we have completed a study of the normal extraocular muscle diameters with ophthalmic echography.

Patients and Methods

The extraocular muscles of 38 healthy subjects were measured at our institution between 1986 and 1991. No subject had a history of thyroid dysfunction, other extraocular muscle disorder, other orbital disease, or diplopia. Eighteen men and 20 women, with a mean age of 47 years (range, 23 to 83 years) were included. Thirty-six subjects were white or mixed Hispanic and two patients were black. The weight and height of each subject were recorded, and also axial eye length measurements were obtained in 22 subjects.

All echographic examinations were performed with the instrumentation and techniques of standardized echography.[5-7] The equipment used included the Ophthascan S (combined B- and standardized A-scan) and, in some cases, the Mini A standardized A-scan instrument (Alcon Surgical, Inc., Fort Worth, Texas).

A combined approach, using both contact B-scan and standardized A-scan instrumenta-

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tion, was used. The superior rectus/levator complex, medial, lateral, and inferior recti muscles were measured in both orbits of all subjects. Although the superior recti and levator palpabrae muscles usually can be displayed as separate structures on B-scan, they are traditionally imaged and measured as a unit complex on A-scan. It is important to include measurement of the levator muscle routinely in the evaluation of patients with suspected orbital disease because the levator muscle may enlarge, particularly in patients with Graves' ophthalmopathy.[8]

The specific examination techniques used to examine the extraocular muscles with standardized echography have been previously described[5-7] but will be summarized here. The compact muscle fiber bundles have a relatively smooth surface, so that a muscle produces a distinct, homogeneous pattern in the orbital echogram (Fig. 1). With the combined approach, B-scan is first performed to evaluate overall size and morphologic characteristics of the extraocular muscles. This includes both transverse (coronal) and longitudinal (radial) images. The transverse orientation provides a cross-sectional (diameter) view, and the longitudinal orientation provides a long-axis (anteroposterior) view of approximately the anterior two thirds of a rectus muscle (Fig. 2). Initial B-scan images assist the echographer in localizing each muscle and provide an impression of overall size.

Standardized A-scan is then used to measure muscle-belly thickness accurately. With the eye in or near primary gaze, the probe is placed on the anesthetized globe in the region of the equator opposite the muscle to be measured. With the gain adjusted to the Tissue Sensitivity

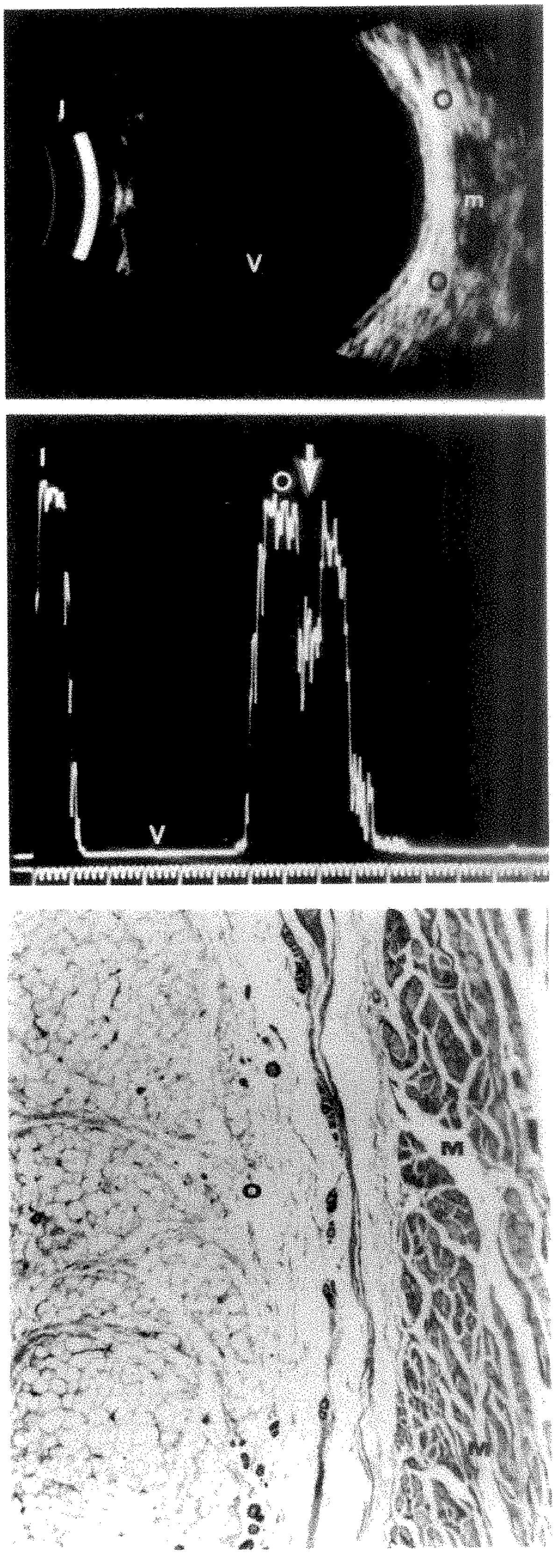

Fig. 1 (Byrne and associates). Echograms and histopathologic characteristics of normal extraocular muscle and orbital soft tissue. Top, B-scan cross section of an extraocular muscle (m) shows distinct, echolucent pattern compared to echo-dense, surrounding orbital tissue (O). I indicates initial line, corresponding to probe face on globe; V indicates vitreous cavity. Middle, Standardized A-scan echogram of cross section of extraocular muscle (arrow) shows lower reflectivity of muscle than surrounding orbital fat (O). I indicates initial spike, corresponding to probe tip on globe; V indicates vitreous cavity. Bottom, Histopathologic view of normal extraocular muscle (M) shows relatively compact muscle fiber bundles with smooth border compared to orbital fat and connective tissue septi (O).

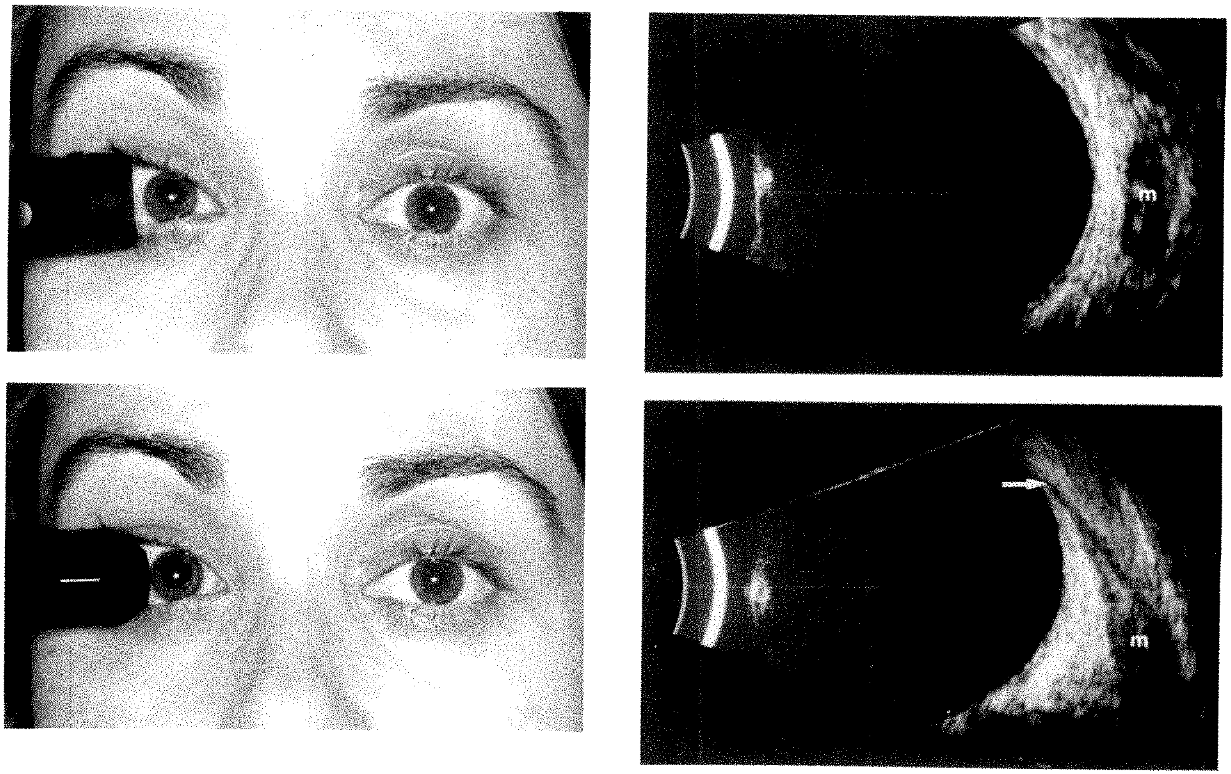

Fig. 2 (Bryne and associates). B-scan technique for displaying the medial rectus muscle. Left top and bottom, The patient is fixating in primary gaze. Right, B-scan echograms of the medial rectus muscle. Top, Vertical transverse scan shows cross section of muscle (m) as oval-shaped echolucent structure. Bottom, Longitudinal scan displays anteroposterior (radial) section of muscle (m) as a wedge-shaped echolucent structure. The muscle extends from its thin, tendinous insertion anteriorly (arrow) toward the orbital apex posteriorly.

setting,[9] the sound beam is first directed across the globe anteriorly to display the tendinous insertion of the muscle into the globe. The sound beam is then angled toward the orbital apex and the muscle pattern is identified posteriorly as far as possible, and it is then traced anteriorly toward the globe (Fig. 3). This dynamic maneuver permits muscle localization, assessment of internal reflectivity, and determination of the area of maximum thickness. The widest diameter of the muscle is then measured, either directly from the display screen using electronic gates, or photographs of the echograms may be measured using calipers and a conversion table. Typically, two independent measurements are obtained for each muscle so that the best quality echogram with the widest measurement is used to derive a final diameter value.

Statistical evaluation of muscle-width data was conducted separately for both right and left orbits. It is widely recognized[10] that right and left eye data are correlated and that observations of two eyes from one individual are not equivalent to observations of one eye each from two people. For this reason, only right orbit data were analyzed. Mainland[11] discussed two methods of determining normal cutoff values for clinical measurements. When the measurements follow a gaussian distribution, the sample mean and standard deviation can be used to generate values that should include approximately 95% of the population. If measurements do not follow a gaussian distribution, percentage points calculated directly from the sample may be used. We used each of these methods in the appropriate situations.

The distributions of muscle diameters were tested for deviation from a gaussian distribution using the Shapiro-Wilks[12] and Kolmogorov-Smirnov[13] tests. The distribution of absolute values of the interocular difference in measurements between contralateral muscles would not be expected to be gaussian.[14] The effects of categoric demographic variables (gender, for example) on the muscle sizes, and the contralateral differences between muscle measurements, were both examined with the two-

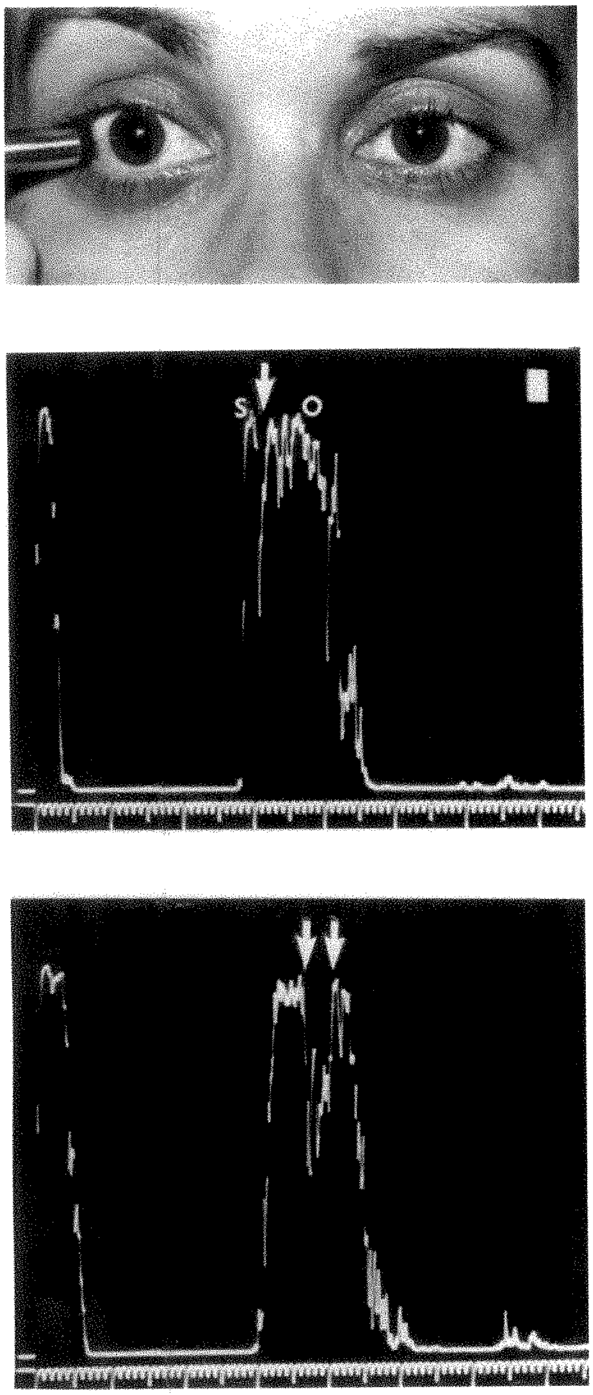

Fig. 3 (Byrne and associates). A-scan technique for examining the medial rectus muscle. Top, The patient fixates in primary gaze and the A-scan probe is placed on the globe temporally, near the equator. Middle, Echogram of tendinous insertion of muscle anteriorly (arrow); S indicates sclera; O indicates orbital soft tissue. Bottom, Echogram of widest portion of muscle belly. Maximal diameter of this muscle is 3.1 mm, measured between steeply rising spikes produced by muscle surface (arrows).

sample *t*-test[15] and the Mann-Whitney test.[16] We calculated for correlations between muscle-size measurements, and for interocular differences, with continuous demographic variables (age, weight, and height) using both Pearson's correlation[17] and Kendall's rank correlation.[18]

Ninety-five percent normal cutoffs for the muscle diameters were computed by adding (and subtracting) two times the standard deviation from the mean. Some authors[11] have recommended using percentiles to determine normal ranges. In this study of 38 subjects, the 95th percentile upper and lower limits are approximately equal to the maximum and minimum. These values are similar to the limits that were obtained by using the means and standard deviations. Because the distributions of the absolute values of the difference between contralateral muscle measurements could not be expected to follow a gaussian distribution, cutoffs were determined by using the 95th percent point.

Results

The derived muscle diameter measurement data from this study were analyzed (Table 1). The analysis of our data provided the following three mechanisms to evaluate the thickness of the extraocular muscles: a range of normal diameters for each of the four muscles and a combined numerical index for all muscles in one orbit (Table 2), and acceptable interocular differences in diameter between contralateral fellow muscles (Table 3). The goodness-of-fit tests that were used gave little indication, in this small sample, that the distributions of muscle sizes were nongaussian. Only data from the right lateral rectus muscle (Fig. 4) showed significant departure from a gaussian fit ($P = .013$).[12]

We found no consistent correlation with any of the demographic variables (gender, race, age, height, and weight) in these subjects when considering the size of muscles in either the right or left orbits, or the differences between muscle pairs. Data obtained in only two black subjects did not vary from the other subjects studied. Age was found to be positively correlated with muscle size in both right ($r = .36$, $P = .03$) and left ($r = .32$, $P = .06$) superior recti muscles (that is, superior recti muscles tended to be larger in the older subjects). Additionally, the absolute value in the contralateral size

TABLE 1
DIAMETERS OF HEALTHY EXTRAOCULAR MUSCLES*

MUSCLE	MEAN ± STANDARD DEVIATION (MM)	MEDIAN
Superior rectus/levator complex (37 subjects)		
Muscle diameter	5.3 ± 0.7	5.4
Difference	0.3 ± 0.3	0.2
Lateral rectus muscle (38 subjects)		
Muscle diameter	3.0 ± 0.4	3.1
Difference	0.1 ± 0.1	0.1
Inferior rectus muscle (38 subjects)		
Muscle diameter	2.6 ± 0.5	2.6
Difference	0.2 ± 0.2	0.1
Medial rectus muscle (37 subjects)		
Muscle diameter	3.5 ± 0.6	3.6
Difference	0.2 ± 0.2	0.2
Sum of all muscles (36 subjects)		
Muscle diameter	14.4 ± 1.3	14.6
Difference	0.5 ± 0.4	0.4

*Muscle sizes determined using right orbit data. Summary of statistics for all subjects showing muscle diameters and the absolute value of the interocular difference between contralateral muscles.

differences between the lateral recti muscles also correlated positively with age (r = .39, P = .016). The nonparametric correlations supported the Pearson correlation analysis.[17]

In 22 patients axial eye length measurements were recorded. The mean and standard deviation of the axial lengths was 23.7 ± 1.2 mm (minimum, maximum: 21.8 mm, 27.0 mm) for right eyes and 23.6 ± 1.1 mm (minimum, maximum: 21.7 mm, 25.7 mm) for left eyes. Axial eye length was significantly inversely correlated with the diameter of the lateral rectus muscle (R.E.: r = −.5, P = .02; L.E.: r = −.41, P = .056). In other words, thinner lateral recti muscles were found in eyes with longer axial eye length measurements. The contralateral difference in axial eye length also correlated with the contralateral difference in thickness of the lateral recti muscles.

Discussion

In 1977, McNutt, Kaefring, and Ossoinig[4] first reported A-scan ultrasound values for extraoc-

TABLE 2
RANGE OF DIAMETERS OF HEALTHY EXTRAOCULAR MUSCLES*

MUSCLE	NORMAL RANGE (MM)
Superior rectus/levator complex	3.9–6.8
Lateral rectus muscle	2.2–3.8
Inferior rectus muscle	1.6–3.6
Medial rectus muscle	2.3–4.7
Sum of all muscles	11.9–16.9

*Muscle sizes determined using right orbit data. Upper and lower normal (95%) ranges for muscle diameters (on the basis of the mean ± 2 standard deviations).

TABLE 3
DIAMETER DIFFERENCES FOR CONTRALATERAL MUSCLES*

MUSCLE	95TH PERCENTILE (MM)
Superior rectus/levator complex	0.8
Lateral rectus muscle	0.4
Inferior rectus muscle	0.4
Medial rectus muscle	0.5
Sum of all muscles	1.2

*Muscle sizes determined using right orbit data. Ninety-fifth percentile limits on the absolute value of the interocular difference between muscles.

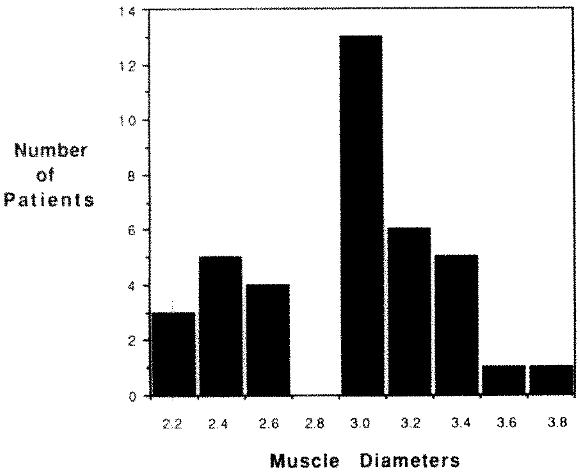

Fig. 4 (Byrne and associates). Histogram of lateral rectus muscle measurements obtained from the right eye of study patients.

ular rectus muscle thickness in the normal population. These normative data established the standards for muscle thickness with standardized A-scan (Kretztechnik 7200 MA A-scan unit). In the McNutt, Kaefring, and Ossoinig study, preliminary contact B-scan assessment of muscle size and location was not performed. Our study included the addition of B-scan techniques to allow a more reliable, efficient A-scan evaluation of the recti muscles.[5-7] Also, patients in the McNutt, Kaefring, and Ossoinig study were examined with the Kretztechnik 7200 MA standardized A-scan instrument, whereas newer standardized A-scan instrumentation was used in our study. The newer instruments now offer freeze-frame capabilities and electronic measurements to provide consistent, accurate measurements of extraocular muscle size.

As described, all measurements in our study were obtained by using a combined B- and A-scan approach, with the specific examination techniques and instrumentation of standardized echography as previously detailed. It is possible that normal muscle values may vary somewhat if different examination techniques and instrumentation are used. Consequently, laboratory-specific normal values must be established if alternative echographic techniques and equipment are used to evaluate the extraocular muscles.

Two of the three standards for assessing muscle size were used, as in the original study by McNutt, Kaefring, and Ossoinig.[4] These included values for the individual muscles and interocular differences between paired contralateral muscles. We added a third standard for evaluating muscle size, a summation of all muscle diameters in a given orbit (Table 2). We postulate that this overall value may be an additionally useful index of muscle thickness, and it may be particularly applied in cases of Graves' orbitopathy in which individual muscle enlargement is minimal, or measurements tend to fluctuate from one examination to the next.[19,20] In these patients, calculation of an overall decrease or increase in muscle-size index may prove clinically reliable.

Although the sample size in our study was relatively small, we found demographic factors to be largely unrelated to muscle sizes so that all data were pooled to obtain one set of normal values. Of numerous statistical tests performed, only age was associated with the muscle-size measurements and only in one of the muscles studied; future investigations of normal muscle size should assess this factor as well as the issue of race, which was not addressed in our study.

Other studies of normal extraocular muscle diameters have been performed using contact B-scan and computed tomographic scanning. Magnetic resonance imaging has been used previously to evaluate the signal characteristics of the extraocular recti muscles in patients with Graves' disease.[21]

In the B-scan studies, performed through the patient's closed eyelids, Willinsky, Arenson, and Hurwitz[22] measured the medial and lateral recti muscles of 16 subjects, whereas Given-Wilson, Pope, and Michell[23] measured only the medial recti muscles of 21 subjects. Both authors provided ranges for the normal medial rectus muscle with somewhat smaller diameters than those reported here. These differences may be explained by variations in the methods used to examine and measure the muscles.

Computed tomographic scanning has also been used to evaluate both the volume and the diameter of the normal recti muscles. Volumetric measurements have been performed by Feldon and associates[24,25] and Hallin and Feldon[26] using a computed image analyzer. They determined the volume of individual recti muscles and calculated the total volume of the muscles in a given orbit.

In a more recent study of 20 patients by Nugent and associates,[27] computed tomographic scans were magnified and the diameter of the rectus muscle was measured directly from the films. The study was performed in patients with orbital diseases unrelated to Graves' disease (for example, retro-orbital pain, acute visual loss, and the like). Standard mean values for the individual recti muscles and an overall muscle diameter index were established, a concept similar to the total muscle diameter obtained with A-scan echography in our study.

It is not surprising that various techniques of examination and measurement result in different ranges for healthy tissues. Furthermore, it is important to emphasize that normal values must be interpreted according to the methods used.

An arguable advantage of computed tomography and magnetic resonance imaging is that these techniques are more visually interpretable than are echograms. Images of both orbits may be viewed simultaneously to facilitate comparison of muscle size. Furthermore, these imaging methods readily show abnormalities in adjacent periorbital sinuses or in the intracranial space. Also, the orbital apex region is better visualized with computed tomography and magnetic resonance imaging than with echography, in which posterior sound penetration and image resolution are limited.

A great advantage of echography is the facility with which the position of the probe may be redirected, to present the sound beam perpendicular to the structure of interest. Positioning of the probe, under direct visualization, eliminates the possibility of oblique sectioning and spurious measurements, as can occur with computed tomography or magnetic resonance imaging. Furthermore, the ultrasound instrumentation that is now available provides excellent resolution of orbital structures to allow reliable detection and tissue differentiation of most abnormalities. Ultrasound equipment is usually portable so that examinations can be performed in the clinic or at the bedside. Echography is noninvasive, inexpensive, and is potentially available within the ophthalmologist's office or in the eye clinic.

Standardized echography is a practical and accurate method to evaluate the extraocular muscle diameters and to differentiate extraocular muscle disorders.[20,28-31] Measurements are obtained with standardized A-scan after an initial examination of the overall muscle topography with contact B-scan. Echographic differentiation between the various causes of muscle enlargement is determined by whether both orbits are affected, the degree and location of thickening (that is, muscle tendon vs belly), and the internal reflectivity of the involved muscles.[5,6,19,20,30]

Standardized A-scan echography is a practical modality for precisely measuring the diameter of the extraocular recti muscles. The normal values we have provided will allow other examiners to distinguish diseased extraocular muscles from normal extraocular muscles using the same instrumentation and techniques. Furthermore, accurate baseline data may be established to monitor progression or regression of disorders such as Graves' disease or idiopathic orbital myositis.

References

1. Glaser, J. S.: Orbital diseases and neuro-ophthalmology. An overview. In Glaser, J. S. (ed.): Neuro-ophthalmology, ed. 2. Philadelphia, J. B. Lippincott Company, 1990, pp. 453–457.
2. Ossoinig, K. C.: The role of clinical echography in modern diagnosis of periorbital and orbital lesions. In Proceedings of the Third International Symposium on Orbital Disorders. Amsterdam, 1977, 502.
3. ———: The technique of measuring the extraocular muscles. In Gernet, H. (ed.): Diagnostica Ultrasonica in Ophthalmologica. Muenster, Germany, R. A. Remy Verlag, 1979, pp. 166–167.
4. McNutt, L. C., Kaefring, S. L., and Ossoinig, K. C.: Echographic measurement of extraocular muscles. In White, D., and Brown, R. E. (eds.): Ultrasound in Medicine, vol. 3A. Basel, Karger, 1977, pp. 927–932.
5. Byrne, S. F.: Standardized echography of the eye and orbit. Neuroradiology 28:618, 1986.
6. Byrne, S. F., and Glaser, J. S.: Orbital tissue differentiation with standardized echography. Ophthalmology 90:1071, 1983.
7. Ossoinig, K. C.: Standardized echography. Basic principles, clinical applications and results. Int. Ophthalmol. Clin. 19:165, 1979.
8. Small, R. G.: Enlargement of levator palpebrae superioris muscle in Graves' ophthalmopathy. Ophthalmology 96:430, 1989.
9. Till, P., and Ossoinig, K. C.: First experiences with a new solid tissue model for the standardization of A- and B-scan instruments used in tissue diagnosis. In White, D., and Brown, R. E. (eds.): Ultrasound in Medicine. London, Plenum Press, 1977, pp. 2167–2174.
10. Ederer, F.: Shall we count numbers of eyes or numbers of subjects? Arch. Ophthalmol. 89:1, 1973.
11. Mainland, D.: Remarks on clinical "norms." Clin. Chem. 17:267, 1971.
12. Hahn, G. J., and Shapiro, S. S.: Statistical Models in Engineering. New York, John Wiley & Sons, Inc., 1967, pp. 295–298.

13. Bradley, J. V.: Distribution-Free Statistical Tests. Englewood Cliffs, N.J., Prentice-Hall, 1968, pp. 296–303.

14. Leone, F. C., Nelson, L. S., and Nottingham, R. B.: The folded normal distribution. Technometrics 3:543, 1961.

15. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, ed. 8. Ames, Iowa, Iowa State University Press, 1982, pp. 93–94.

16. ———: Statistical Methods, ed. 8. Ames, Iowa, Iowa State University Press, 1982, pp. 142–144.

17. ———: Statistical Methods, ed. 8. Ames, Iowa, Iowa State University Press, 1982, pp. 177–187.

18. ———: Statistical Methods, ed. 8. Ames, Iowa, Iowa State University Press, 1982, p. 194.

19. Ossoinig, K. C.: The role of standardized ophthalmic echography in the management of Graves' ophthalmopathy. In Pickardt, C. R., and Boergen, K. P. (eds.): Developments in Diagnostic Methods and Therapeutical Procedures. Basel, Karger, 1989, pp. 28–32.

20. ———: Ultrasonic diagnosis of Graves' ophthalmopathy. In Gorman, C. A., Waller, R. R., and Dyer, J. A. (eds.): The Eye and Orbit in Thyroid Disease. New York, Raven Press, 1984, pp. 185–211.

21. Hosten, N., Sander, B., Cordes, M. D., and Schubert, C. J.: Graves ophthalmopathy. MR imaging of the orbits. Head Neck Radiol. 172:759.

22. Willinsky, R. A., Arenson, A. M., and Hurwitz, J. J.: Ultrasonic B-scan measurement of the extraocular muscles in Graves' orbitopathy. J. Can. Assoc. Radiol. 35:171, 1984.

23. Given-Wilson, R., Pope, R. M., Michell, M. J., Cannon, R., and McGregor, A. M.: The use of real-time orbital ultrasound in Graves' ophthalmopathy. A comparison with computed tomography. Br. J. Radiol. 62:705, 1989.

24. Feldon, S. E., Lee, C. P., Muramatsu, S. K., and Weiner, J. M.: Quantitative computed tomography of Graves' ophthalmopathy. Extraocular muscle and orbital fat in development of optic neuropathy. Arch. Ophthalmol. 103:213, 1985.

25. Feldon, S. E., and Weiner, J. M.: Clinical significance of extraocular muscle volumes in Graves' ophthalmopathy. A quantitative computed tomography study. Arch. Ophthalmol. 100:1266, 1982.

26. Hallin, E. S., and Feldon, S. E.: Graves' ophthalmopathy. I. Simple CT estimates of extraocular muscle volume. Br. J. Ophthalmol. 72:674, 1988.

27. Nugent, R. A., Belkin, R. I., Neigel, J. M., Rootman, J., Robertson, W. D., Spinelli, J., and Graeg, D. A.: Graves orbitopathy. Correlation of CT and clinical findings. Radiology 177:675, 1988.

28. Holt, J. E., O'Connor, P. S., Douglas, J. P., and Byrne, B. M.: Extraocular muscle size comparison using standardized A-scan echography and computerized tomography scan measurements. Ophthalmology 92:1351, 1985.

29. Shammas, H. J., Minckler, D. S., and Ogden, C.: Ultrasound in early thyroid orbitopathy. Arch. Ophthalmol. 98:266, 1980.

30. Hasenfratz, G.: Standardized echography in Graves' disease. In Ossoinig, K. C. (ed.): Ophthalmic Echography. Dordrecht, The Netherlands, Dr. W. Junk, 1987, pp. 557–564.

31. Ossoinig, K. C., and Hermsen, V. M.: Myositis of extraocular muscles diagnosed with standardized echography. In Hillman, J. S., and Lemay, M. M. (eds.): Ophthalmic Ultrasonography. Dordrecht, The Netherlands, Dr. W. Junk, 1983, pp. 381–392.

OPHTHALMIC MINIATURE

Today, thanks to men like Edison and Franklin, and frogs like Galvani's, we receive almost unlimited benefits from electricity. For example, in the past decade scientists developed the laser, an electronic appliance that emits a beam of light so powerful that it can vaporize a bulldozer two thousand yards away, yet so precise that doctors can use it to perform delicate operations on the human eyeball, provided they remember to change the power setting from "VAPORIZE BULLDOZER" to "DELICATE."

Dave Barry, *Bad Habits, A 100% Fact-Free Book,*
New York, Henry Holt and Co., 1987, p. 174

Visual-evoked Cortical Potentials in Dissociated Vertical Deviation

Alina A. Zubcov, M.D., Michael G. Fendick, Ph.D., Irene Gottlob, M.D.,
Sheryl S. Wizov, and Robert D. Reinecke, M.D.

It is debatable whether chiasmatic misrouting of temporal optic-nerve fibers (similar to that found in ocular albinism) is also characteristic of dissociated vertical deviation. Pattern appearance, pattern reversal, and diffuse-flash, monocular full-field visual-evoked cortical potentials were recorded from albino and normal human subjects and subjects with dissociated vertical deviation. Pattern appearance was the most reliable stimulus for evaluating lateralization (albino-type misrouting) in adult albino patients, and diffuse-flash stimulation was almost as reliable in children. Pattern reversal was found to be an unreliable indicator. Lateralization was not evident among patients with dissociated vertical deviation, as determined by the three modes of stimulation. Our data supported earlier findings that pattern appearance is the most appropriate technique to detect lateralization. Our findings differed from those of previous reports in demonstrating that reliability of the lateralization phenomenon increases with age up to approximately 15 years. Pattern reversal stimulation was not reliable in patients with horizontal nystagmus.

DISSOCIATED VERTICAL DEVIATION is a poorly understood vertical motor disturbance involving an upward rotation and extorsion of one eye and may include latent nystagmus when illumination entering that eye is reduced. Clinically, dissociated vertical deviation is associated with infantile esotropia and is bilateral even if one of the eyes has only minimal vertical deviation. It is difficult to measure this vertical deviation accurately because of the transiently hypotropic position of the fixing eye during the prism uncover test. Dissociated vertical deviation is surgically challenging because of its tendency to recur after an eye muscle operation.

Because this condition has several clinical similarities to albinism, such as nystagmus and lack of stereopsis, authors have studied the symmetry of visual-evoked cortical potentials in patients with dissociated vertical deviation. Although other conditions associated with infantile nystagmus or with strabismus do not involve lateralization (also called increased decussation or albino-type misrouting),[1,2] the lack of binocular vision in albinos and patients with dissociated vertical deviation relates the two entities more than other conditions associated with nystagmus. In addition to albinism, abnormal decussation of the temporal fibers of the retina has been reported in Chediak-Higashi syndrome and chiasmatic lesions.[3,4] A study of visual-evokedcortical potentials in dissociated vertical deviation[5] reported abnormal decussation as seen in albinos in 77.4% of patients with dissociated vertical deviation in response to pattern reversal stimulation of the temporal hemiretina. Two later studies[6,7] contradicted these conclusions using diffuse-flash visual-evoked cortical potentials, and pattern reversal and diffuse-flash visual-evoked cortical potentials, respectively. One study[7] reported markedly smaller monocular cortical potentials in the patients with dissociated vertical deviation. Another study using pattern appearance showed no difference between normal subjects and patients with dissociated vertical deviation.[8]

Most investigators have used different stimulation modes that were not optimal for the lateralization phenomenon (pattern reversal and diffuse flash). We used all three stimulation

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modalities on 11 patients with dissociated vertical deviation, 21 normal subjects, and 14 albinos matched for age and gender in our attempt to determine whether chiasmatic misrouting of temporal optic-nerve fibers similar to that found in albinism is also characteristic of dissociated vertical deviation.

Material and Methods

Eleven patients with dissociated vertical deviation ranging from 6 to 47 years of age (mean age, 23 years) were examined. All had strabismus and five were amblyopic in one eye. One patient was amblyopic in both eyes. The degree of amblyopia was mild (20/20 to 20/30) in four patients and moderate (20/40 to 20/100) in one patient. All patients had latent nystagmus. The control groups consisted of 21 normal subjects ranging from 5 to 52 years of age (mean age, 25 years), and 14 albino patients ranging from 4.5 to 58 years of age (mean age, 24 years). The normal subjects all had 20/20 visual acuity in both eyes and had stereopsis. They had no manifest strabismus, no nystagmus, and no other abnormalities. The albinos all had iris transillumination and various forms of fundus pigmentation ranging from blond fundus with almost normal pigmentation to poor macular pigmentation. No albino had blood vessels crossing the macular areas. Six albino patients were amblyopic, and all had jerk, pendular, or torsional nystagmus at higher intensity than did the patients with dissociated vertical deviation. The degree of amblyopia was mild in one patient, moderate in four patients, and severe in one. Six of 14 patients had strabismus. The refractive error of all patients was corrected while the examination was performed.

Horizontal square-wave gratings were generated by a display processor and displayed on a video monitor (16.80 × 13.55-degree rectangular display field at 1 meter) at 97% contrast and 29.55 candelas/m^2 mean luminance. We used a bar size and spacing of 64.86 minutes of an arc = 0.46 cycles/degree, which is comparable to the 55 minutes of an arc optimum reported by Apkarian and associates[9] to detect lateralization within the C1 component. Most investigators using pattern stimulation used checkerboard patterns, even though many patients had horizontal nystagmus. To avoid orientation-specific effects, we used only horizontal gratings. The stimulation mode was pattern appearance at 1.25 Hz to provide 60 records in 45 seconds of viewing time and pattern reversal and diffuse-flash mode at 2.0-Hz stimulation with a 2.0-Hz analysis frequency so that 60 records were obtained in 30 seconds of viewing time. Flash stimuli were delivered by a xenon flash photostimulator. The viewing distance was 50 cm for the flash stimuli and 1 meter for the other two stimulation modes.

We recorded the response to full-field stimulation on two channels with the active electrodes 1 cm above the inion and 5 cm to either side of OZ, each referenced to a single electrode at CZ, with the ground electrode placed on the left ear. Signals thus obtained were amplified by two AC-coupled preamplifiers with ½ amplitude bandpass settings of 0.1 to 30 Hz and gain of 50,000. The resulting electroencephalogram was sampled at 80 Hz by the evoked potential recording system. Subjects were tested monocularly under subdued room illumination using pattern appearance, pattern reversal, and diffuse-flash stimulation with two complete recordings per eye under each of the three conditions. To avoid short-term adaptation and fatigue influences, the eight pattern trials of both eyes were performed with pattern appearance alternating with pattern reversal succeeded by four flash trials, alternating the viewing eye. All digitized raw data were stored for subsequent analysis.

The difference between corresponding sampled points of the visual-evoked cortical potential waveforms recorded at the contralateral and ipsilateral scalp electrodes was defined as lateralization. A mean lateralization value was calculated at each point as half the sum of the lateralization value from each eye. Two lateralization indices were defined by reference to the array of mean lateralization values. One was the maximal lateralization value within the range of 75 to 125 milliseconds after stimulus onset, whereas the second index was defined as the maximal lateralization value within the 75- to 250-millisecond range. The use of two lateralization indices was necessary so both peaks could be measured in the mean diffuse-flash stimulation mode. Each lateralization index of the three groups was classified as normal if it fell within 2 standard deviations above the mean of normal subjects, and was classified as abnormal if it exceeded this criterion. Sensitivity and specificity of the lateralization phenomenon were calculated for each of the three stimulation modes using the albino and normal subjects. To prove a significant difference between the groups examined (albinos vs normal subjects and patients with dissociated vertical deviation) regarding frequency of lateralization, we used a one-factorial analysis of variance for multiple measurements at 99% confidence interval.

Results

Analysis of the data showed an obvious difference between subjects 15 years of age and younger and subjects older than 15 years of age. No other correlations (degree of visual acuity loss, nystagmus intensity, for example) were apparent. Therefore, we used the two subgroups of subjects older than 15 years of age and those 15 of age and younger for subsequent age comparisons.

Mean lateralization and lateralization index—The mean lateralization calculated as described was analyzed in waveform in the normal subjects, patients with dissociated vertical deviation, and the albino group older than 15 years of age in response to pattern appearance stimulation (Fig. 1). The data of the subjects 15 years of age and younger were also analyzed (Fig. 2). Lateralization in the normal subjects and patients with dissociated vertical deviation was not significant as opposed to that of the albino group. The lateralization was observed to be larger and more variable in the younger albino group than in the albinos more than 15 years old. The visual-evoked cortical potentials in response to diffuse-flash stimulation were determined in subjects older than 15 years of age (Fig. 3) and subjects 15 years of age and younger (Fig. 4). The patients with dissociated vertical deviation did not have marked lateralization. The albino group had two lateralization peaks that were both less pronounced than the single peak in the pattern appearance data. Similar lateralization was seen among normal subjects in response to diffuse-flash stimulation. The mean lateralization values of the visual-evoked cortical potentials in response to pattern reversal stimulus were determined (Figs. 5 and 6). None of the three groups had marked lateralization.

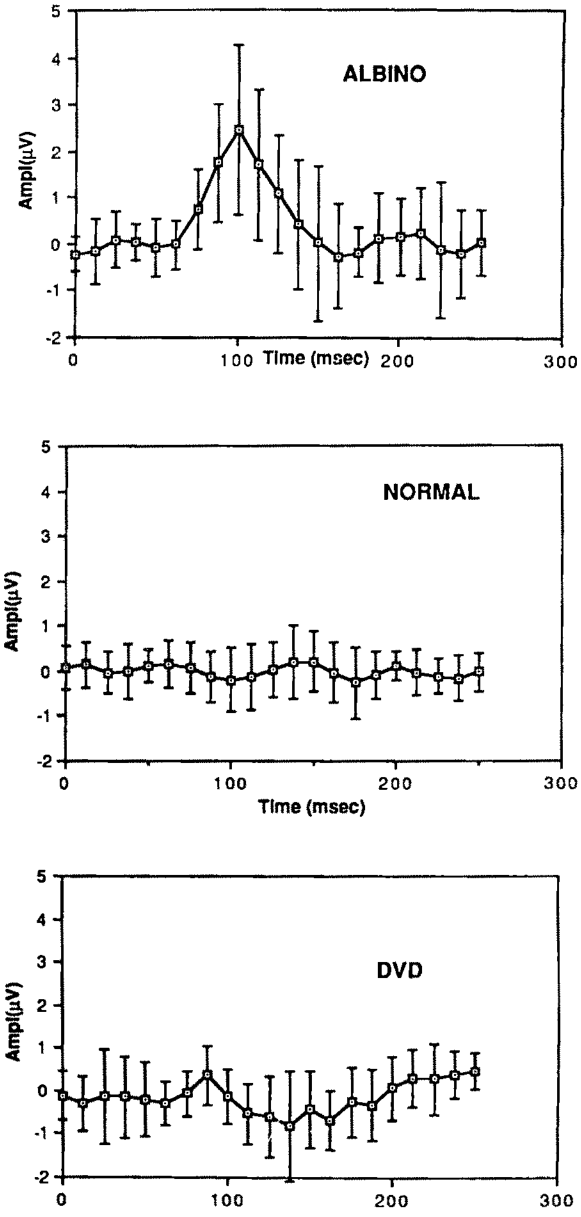

Fig. 1 (Zubcov and associates). Mean lateralization in response to pattern appearance stimulus in albinos (top), normal subjects (middle), and patients with dissociated vertical deviation (bottom) older than 15 years of age. On the abscissa, the time is recorded in milliseconds after the stimulation and on the ordinate, the amplitude is recorded in microvolts. DVD indicates dissociated vertical deviation.

The sensitivity and specificity of the lateralization index within both the 75- to 125- and 75- to 250-millisecond ranges for each of the stimulation modes were determined (Fig. 7). Figure 7, left, shows results from subjects older than 15 years of age and Figure 7, right, shows results from subjects 15 years of age and younger. Pattern appearance had a high sensitivity and specificity in the older group, whereas it appeared slightly less effective in younger subjects than it did in adults. The later lateraliza-

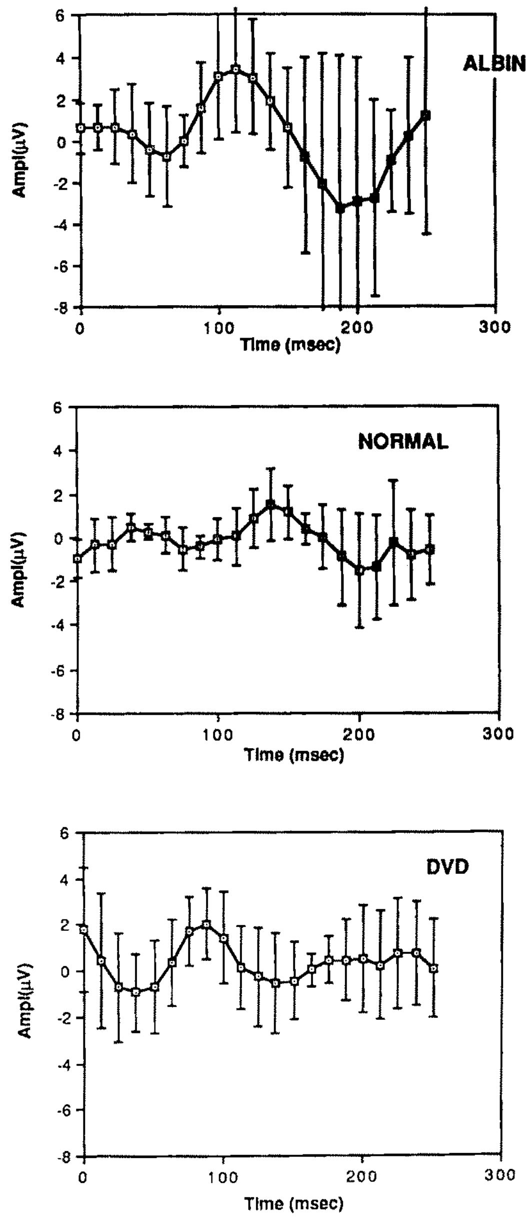

Fig. 2 (Zubcov and associates). Mean lateralization in response to pattern appearance stimulus in albinos (top), normal subjects (middle), and patients with dissociated vertical deviation (bottom) 15 years of age and younger. On the abscissa, the time is recorded in milliseconds after the stimulation and on the ordinate, the amplitude is recorded in microvolts. DVD indicates dissociated vertical deviation.

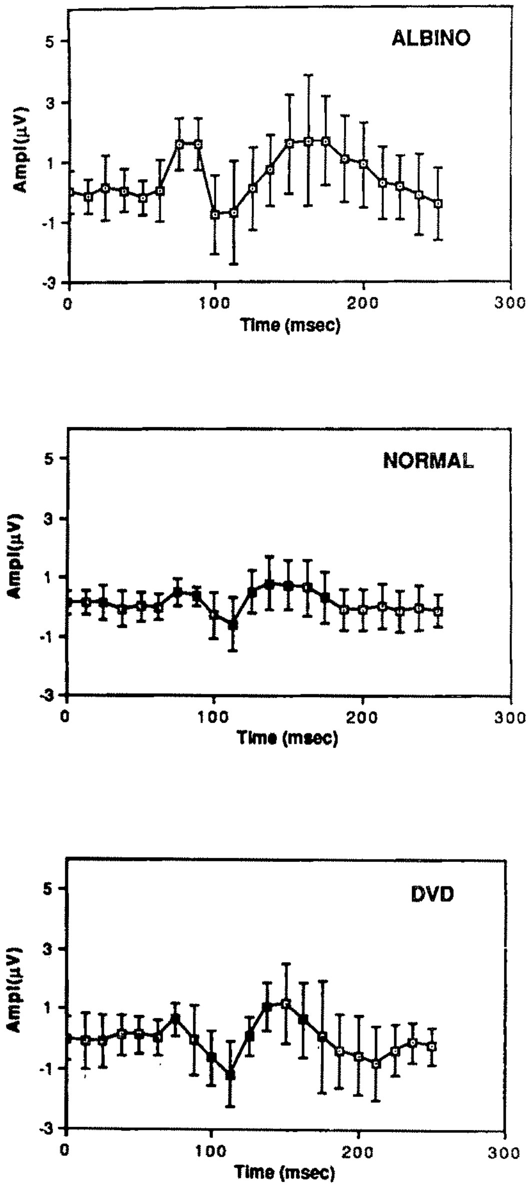

Fig. 3 (Zubcov and associates). Mean lateralization in response to diffuse flash stimulus in albinos (top), normal subjects (middle), and patients with dissociated vertical deviation (bottom) older than 15 years of age. On the abscissa, the time is recorded in milliseconds after the stimulation and on the ordinate, the amplitude is recorded in microvolts. DVD indicates dissociated vertical deviation.

tion peak derived from flash retained its sensitivity in both age groups. The pattern reversal stimulation mode proved to be remarkably insensitive given our criterion of falling within 2 standard deviations above normal subjects. In the pattern appearance and diffuse-flash modes of stimulation, lateralization was statistically significant (P = .0001 and P = .0047, respectively) in the albino group. In response to pattern reversal stimulation, no statistically significant lateralization was detected. The patients with dissociated vertical deviation did not have

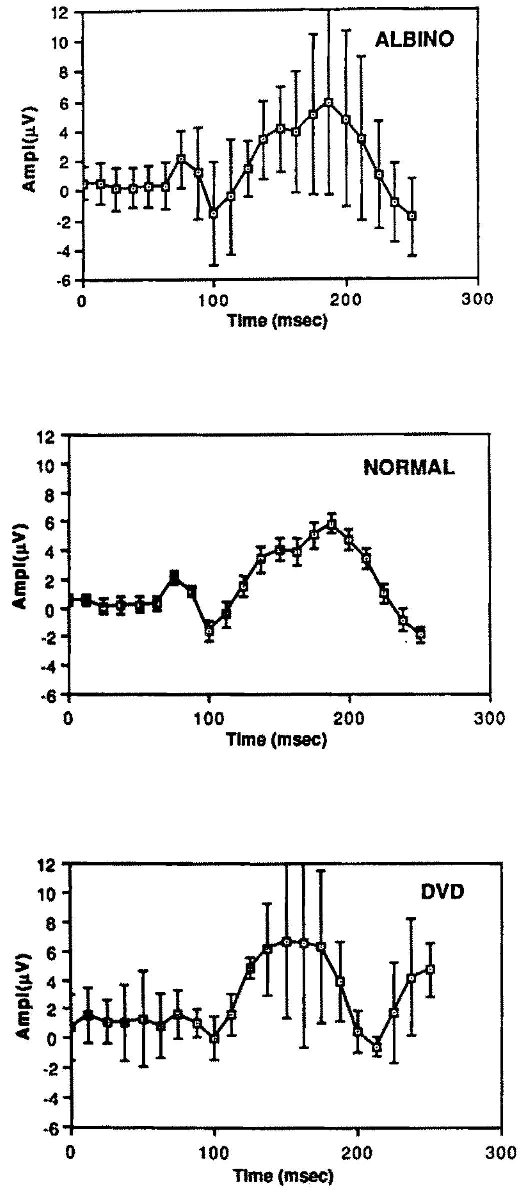

Fig. 4 (Zubcov and associates). Mean lateralization in response to diffuse-flash stimulus in albinos (top), normal subjects (middle), and patients with dissociated vertical deviation (bottom) 15 years of age and younger. On the abscissa, the time is recorded in milliseconds after the stimulation and on the ordinate, the amplitude is recorded in microvolts. DVD indicates dissociated vertical deviation.

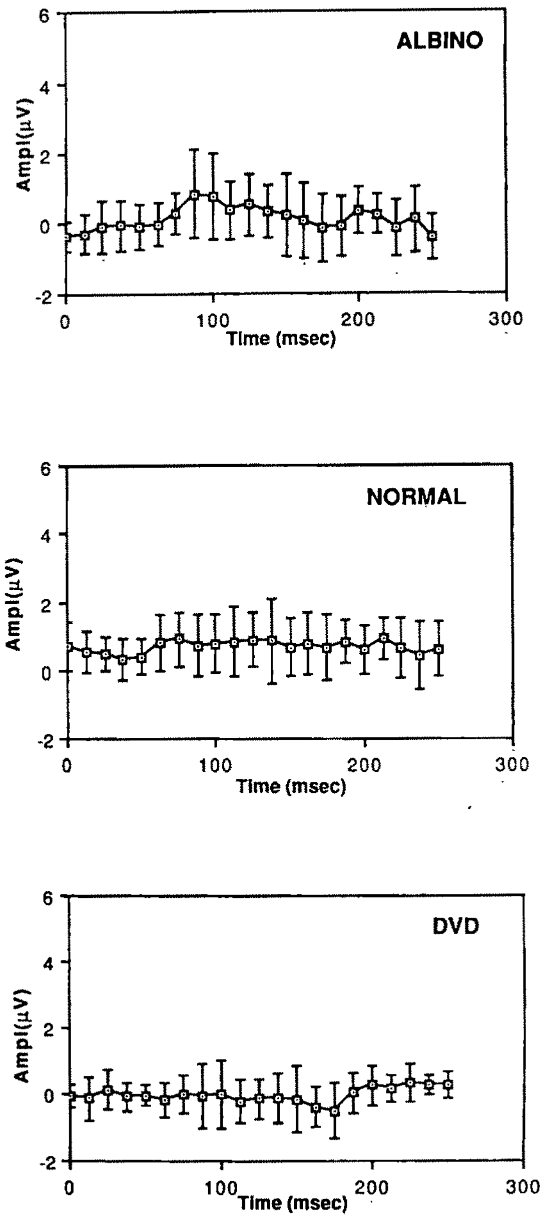

Fig. 5 (Zubcov and associates). Mean lateralization in response to pattern reversal stimulus in albinos (top), normal subjects (middle), and patients with dissociated vertical deviation (bottom) older than 15 years of age. On the abscissa, the time is recorded in milliseconds after the stimulation and on the ordinate, the amplitude is recorded in microvolts. DVD indicates dissociated vertical deviation.

lateralization in response to any mode of stimulation.

The test outcome by age for the two lateralization indices is seen in Figure 8. Results of a test were positive if the lateralization index fell outside 2 standard deviations above the mean of normal subjects. Again, the patients with dissociated vertical deviation had a normal test outcome with the exception of two subjects, both younger than 15 years of age, for whom results of a pattern appearance test for the 75- to 125-millisecond lateralization index were positive.

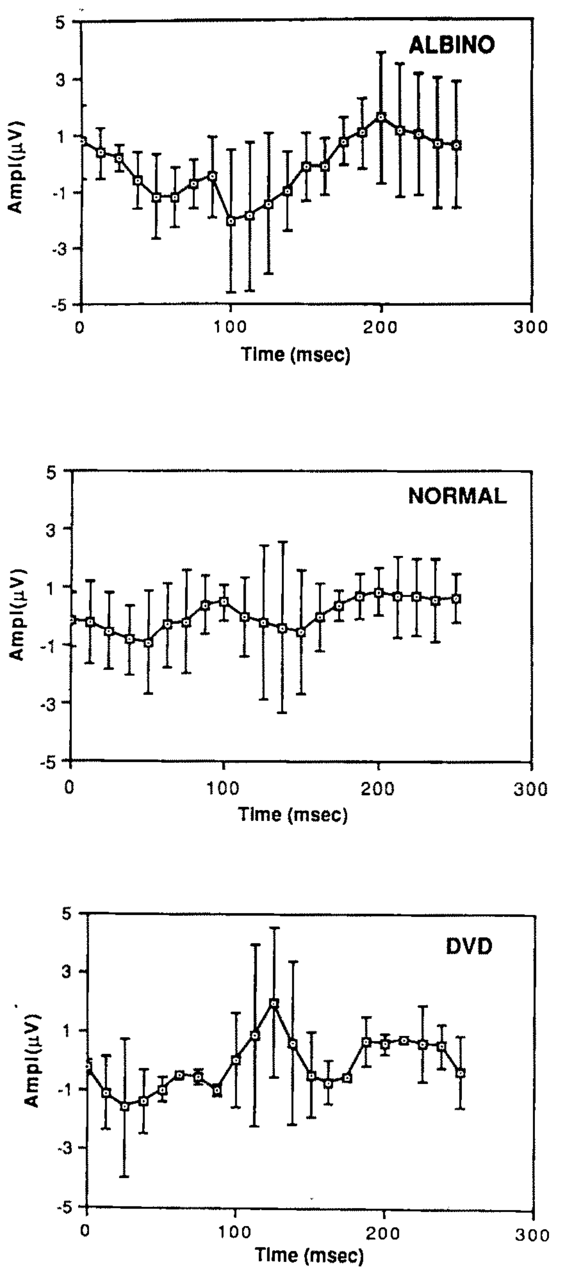

Fig. 6 (Zubcov and associates). Mean lateralization in response to pattern reversal stimulus in albinos (top), normal subjects (middle), and patients with dissociated vertical deviation (bottom) 15 years of age and younger. On the abscissa, the time is recorded in milliseconds after the stimulation and on the ordinate, the amplitude is recorded in microvolts. DVD indicates dissociated vertical deviation.

Amplitudes of the P100—We analyzed the amplitudes of the P100 in response to pattern reversal stimuli. The values of the P100 were recorded at the ipsilateral hemisphere. Albino subjects and subjects with dissociated vertical deviation had lower amplitude pattern reversal responses than the normal subjects, which was statistically significant only in the albinos. Within the normal group, the subgroup of subjects 15 years of age and younger had higher amplitudes than the subgroup of subjects older than 15 years of age. Within the group of patients with dissociated vertical deviation, the subgroup of patients 15 years of age and younger had a higher amplitude of the P100 in the eye with better visual acuity than in the eye with worse visual acuity. The older patients with dissociated vertical deviation did not have lower amplitudes than older normal subjects, with the eye with worse visual acuity having lower amplitudes than the eye with better visual acuity. Within the albino group, the differences between the eyes with better and worse visual acuity and between the two age groups were small. Differences between the albino and the other two groups were significant (P = .011). No significant difference was found between the eye with better visual acuity and the eye with worse visual acuity in all three groups, between the age groups, and between the patients with dissociated vertical deviation and normal subjects.

Discussion

Mean lateralization, lateralization index, test outcome—Our findings in the albino group are in general agreement with previous findings reported by Apkarian and associates.[9,10] The visual-evoked cortical potentials elicited by pattern appearance were effective in detecting the kind of lateralization thought to reflect albinotic retinogeniculate pathway abnormalities and were more reliable than those elicited by either diffuse-flash or pattern reversal stimulation. Pattern reversal stimulation proved to be remarkably unreliable for distinguishing albinos from nonalbinotic patients, thereby confirming findings by Apkarian and associates.[9,10] Because pattern appearance was previously shown to be the most reliable test for detecting lateralization, we used this mode. The only study[8] using pattern appearance to investigate lateralization in patients with dissociated vertical deviation had reported no lateralization in the group with dissociated vertical deviation as opposed to the albino group. The other three studies[5-7] used pattern reversal or diffuse-flash,

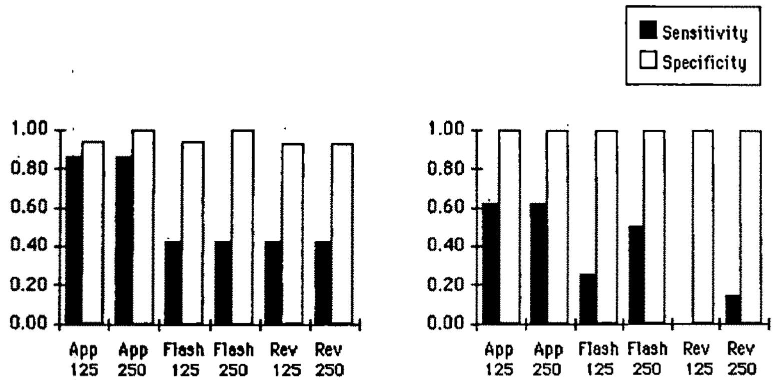

Fig. 7 (Zubcov and associates). Sensitivity and specificity of the three modes of stimulation were calculated in the albino and normal groups (over 15 years of age subgroup depicted on the left, 15 years of age and younger subgroup on the right). Sensitivity was defined as the patients having lateralization divided by the patients with albinism (true positives/true positives + false negatives). Specificity was defined as the patients not having lateralization divided by the normal patients (true negatives/true negatives + false positives). The abscissa shows both lateralization indices for each mode (App indicates appearance, Flash indicates diffuse flash, and Rev indicates pattern reversal); the ordinate gives percentage of sensitivity and specificity in arbitrary units (1.00 = 100%).

or both, as stimulation modes. None of these studies used all three modes of stimulation in albinos and patients with dissociated vertical deviation, so no final conclusion about the patients with dissociated vertical deviation could be made. We did not find lateralization in the patients with dissociated vertical deviation, as determined by the pattern appearance stimulation mode, the most sensitive and specific method (Figs. 1 and 2). We also did not detect lateralization with the diffuse-flash and pattern reversal modes (Figs. 3 through 6). This confirmed findings by Boylan, Clement, and Howrie[6] and Kriss and associates.[7] Additionally, we did not find any marked lateralization in our albino group as determined by pattern reversal stimulation. In contrast, Fitzgerald and Billson[5] found lateralization in a group with dissociated vertical deviation as opposed to normal subjects and a control group with con-

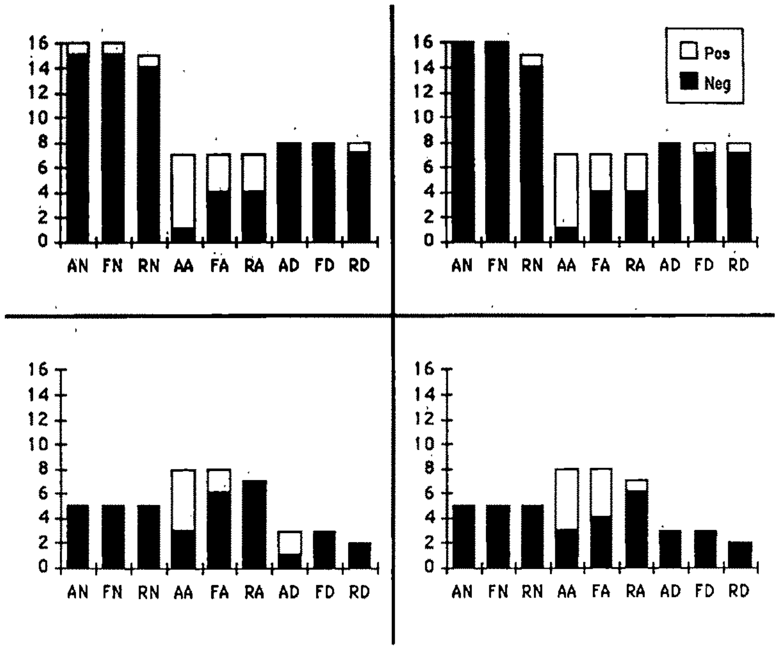

Fig. 8 (Zubcov and associates). Test outcome by age. On the abscissa, the three modes of stimulation A (appearance), F (diffuse flash), and R (pattern reversal) are shown for each of the following three groups of subjects: N (normal subjects), A (albinos), and D (patients with dissociated vertical deviation). The number of patients is shown on the ordinate. Upper panels show the positive and negative results in the subgroup of subjects older than 15 years of age for the 75- to 125-millisecond (left) and the 75- to 250-millisecond lateralization index (right); the lower panels show the same results for the subgroup of subjects 15 years of age and younger.

genital strabismus using pattern reversal checkerboard half-field stimulation. They, however, did not test albino patients to demonstrate the sensitivity of their methods. They also used half-field stimulation without controlling for the latent nystagmus of their patients. The so-called half-field stimulation might have accounted for the lateralization found in their patients with dissociated vertical deviation. Also, the authors did not report the age of their patients, which seemed to have an important role in the detection of lateralization as our results show.

Pattern appearance remains the optimal electrophysiologic screening test for abnormal decussation of temporal retinal fibers to the contralateral geniculate nucleus in albinos. Our patients with dissociated vertical deviation did not have marked lateralization. What differentiates albinism from other clinical syndromes with hypopigmentation or nystagmus, or both, is the disruption of the normal histogenesis of the retina and optic tract caused by the specific albino mutation.

Comparing the visual-evoked cortical potentials of the subgroup of subjects 15 years of age and younger and the subgroup of subjects older than 15 years of age, we determined that the reliability of the lateralization phenomenon increases with age up to approximately 15 years and then remains stable. This appeared to be related to maturation of the visual-evoked cortical potentials. Influence of other factors, such as strabismic amblyopia or nystagmus, was slight with pattern appearance and diffuse-flash stimulation.

Amplitude of P100 in response to pattern reversal stimuli—The amplitudes of pattern appearance and diffuse-flash visual-evoked cortical potentials were not different between the three groups. The amplitudes of the visual-evoked cortical potentials in response to pattern reversal stimulation were markedly smaller in albinos than in normal subjects and patients with dissociated vertical deviation. Because we alternated testing of each eye and the order of pattern appearance and pattern reversal stimulation, the poorer amplitude of pattern reversal visual-evoked cortical potentials cannot be attributed to either adaptation or fatigue. Several random interviews, however, showed that none of the normal subjects had any difficulties with the test, whereas every albino and patient with dissociated vertical deviation interviewed had difficulties in keeping their attention on the pattern reversal stimulus. All our patients with dissociated vertical deviation and all our albino subjects had some degree of horizontal nystagmus with the monocular testing conditions used with the albino group who had more intense nystagmus. The poor responses were probably related to the horizontal jerk and pendular nystagmus predominant in the albinos and to the latent nystagmus (horizontal jerk nystagmus) in the albinos and the patients with dissociated vertical deviation to a lesser extent. Nystagmus seems to influence primarily responses to pattern reversal stimulation, because responses to the other stimulation modes were not affected. Because no marked difference between the eye with better visual acuity and the eye with worse visual acuity in any of the three groups was seen, amblyopia did not appear to have an important role. Kriss and associates[7] found markedly smaller pattern visual-evoked cortical potentials in patients with dissociated vertical deviation compared to the visual-evoked cortical potentials in control subjects and attributed this to amblyopia or nystagmus. We found a stronger correlation of this finding to nystagmus than to amblyopia. The extent of the effect of amblyopia or nystagmus on visual-evoked cortical potential amplitude was speculative because the albino group not only had more intense nystagmus than the patients with dissociated vertical deviation, but also a higher degree of amblyopia. Also, amblyopia is known to attenuate the amplitude of pattern visual-evoked cortical potential but not of pure luminance visual-evoked cortical potential. Recent evidence for abnormal motion discrimination has been reported in association with infantile esotropia[11] and infantile nystagmus.[12] It is well known that pattern reversal stimuli contain strong motion components that stimulate motion-specific visual subsystems.[13] This further supports our suggestion that nystagmus is primarily responsible for the lower P100 amplitude. Contours perpendicular to the direction of nystagmus in checkerboard-patterned stimuli used by others with pattern reversal stimulation is also known to decrease the amplitude and reliability of the visual-evoked cortical potentials of patients with nystagmus.[14,15] To avoid orientation-specific effects, we used only horizontal gratings and still found poor pattern reversal stimulation responses. This study emphasized the importance of carefully choosing stimulation modes, recording variables, and testing conditions when using visual-evoked cortical potentials.

References

1. Guo, S., Reinecke, R. D., Fendick, M., and Calhoun, J. H.: Visual pathway abnormalities in albinism and infantile nystagmus. VECPs and stereoacuity measurements. J. Pediatr. Ophthalmol. Strabismus 26:97, 1989.
2. McCormack, G. L.: Electrophysiologic evidence of normal optic nerve fiber projection in normally pigmented squinters. Invest. Ophthalmol. Vis. Sci. 14:931, 1975.
3. Creel, D., Collier, L. L., Lewenthal, A. G., Conlee, J. W., and Prieur, D. J.: Abnormal retinal projections in cats with Chediak-Higashi syndrome. Invest. Ophthalmol. Vis. Sci. 23:798, 1982.
4. Halliday, A. M., Halliday, E., Kriss, A., McDonald, W. I., and Mushin, J.: The pattern-evoked potential in compression of the anterior visual pathways. Brain 99:357, 1976.
5. Fitzgerald, B. A., and Billson, F. A.: Dissociated vertical deviation. Evidence of abnormal visual pathway projection. Br. J. Ophthalmol. 68:801, 1984.
6. Boylan, C., Clement, R. A., and Howrie, A.: Normal visual pathway routing in dissociated vertical deviation. Invest. Ophthalmol. Vis. Sci. 29:1165, 1988.
7. Kriss, A., Timms, T., Elston, J., Taylor, D., and Gresty, M.: Visual evoked potentials in dissociated vertical deviation. A reappraisal. Br. J. Ophthalmol. 73:265, 1989.
8. Bach, M., and Kommerell, G.: Das Überwiegen kreuzender sehnervenfasern ist ein charakteristikum des albinismus, aber nicht der dissoziierten vertikaldeviation. Fortschr. Ophthalmol. 86:253, 1989.
9. Apkarian, P., Reit, D., Spekreijse, H., and van Dorp, D.: A decisive electrophysiological test for human albinism. Electroencephalogr. Clin. Neurophysiol. 55:513, 1983.
10. Apkarian, P., and Spekreijse, H.: The VEP and misrouted pathways in human albinism. In Cracco, R. Q., and Bodis-Wollner, I. (eds.): Frontiers of Clinical Neuroscience. Evoked Potentials, vol. 3. New York, Alan R. Liss, Inc., 1986, pp. 211–226.
11. Norcia, A. M., Garcia, H., Humphry, R., Holmes, A., Hamer, R., and Orel-Bixler, D.: Anomalous motion VEPs in infancy and esotropia. Invest. Ophthalmol. Vis. Sci. 32:436, 1991.
12. Dieterich, M., and Brand, T. H.: Impaired motion perception in congenital nystagmus and acquired ocular motor palsy. Clin. Vis. Sci. 1:337, 1987.
13. Kulikowsky, J.: Separation of occipital potentials related to the detection of pattern and movement. In Desmedt, J. E. (ed.): Visual Evoked Potentials in Man. New Developments. Oxford, Clarendon Press, 1977, pp. 184–196.
14. Guo, S., Fendick, M. G., and Reinecke, R. D.: Infantile nystagmus. Grating acuity measured using swept spatial frequency VEPs and psychophysics. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 346.
15. Abadi, R. V., and King-Smith, P. E.: Congenital nystagmus modifies orientational detection. Vision Res. 19:1409, 1979.

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EDITORIALS

THE AMERICAN JOURNAL OF OPHTHALMOLOGY: 1965–1991

Frank W. Newell

THE AMERICAN JOURNAL OF OPHTHALMOLOGY first appeared in 1884 with Adolph Alt of St. Louis as editor and, for many years, its chief contributor. It was the first monthly ophthalmic journal in the United States. The Archives of Ophthalmology, which Herman Knapp originated in 1869, was published quarterly. Alt's poor health in 1917 led him to join THE JOURNAL with the Ophthalmic Year Book, edited by Edward Jackson, of Denver, and the Ophthalmic Record, edited by Casey A. Wood, of Chicago. This was the major consolidation of United States ophthalmic journals to form the third series of THE JOURNAL. Wood, who was scheduled to become editor, joined the army in 1917 and Jackson became editor. The business management remained with Wood's colleagues in his Chicago practice. Between 1918 and 1940, Jackson (1918–1927), Crisp (1928–1931), and Post (1931–1940) edited THE JOURNAL. Vail became editor in 1940, and I had the great privilege to succeed him in 1965. Business matters were managed in Chicago until Post became editor in 1931 and were transferred to Cincinnati with Vail and then followed him to Chicago with his appointment to Northwestern University Medical School.

Ophthalmology and THE JOURNAL have undergone an enormous change since 1965. In my chairman's address to the Section of Ophthalmology of the American Medical Association, I predicted the need for some 15,000 ophthalmologists, and a greatly expanded group of skilled ophthalmic assistants, for a United States population of 265 million people.[1] The prediction, like many, was premature and the growth of ophthalmologists and technicians outstripped the population growth, but not the expanded skills and needs of the specialty. Advocacy for the formation of a National Eye Institute was followed shortly thereafter by the political muscle of Jules Stein and Research to Prevent Blindness to make this a reality. After more than a century, the American Medical Association dissolved its specialty sections and thus lost many of its direct connections with specialists. In 1979, a separate American Academy of Ophthalmology emerged, something undreamed of in 1965, and it has become the voice for organized ophthalmology. Ophthalmic efforts in philanthropy have paled except for Research to Prevent Blindness, which has become dominant in the field.

The shelf space filled with volumes 60 to 112, published under my editorship since 1965, awes me with the enormous contribution made by so many to the success of THE JOURNAL. As an independent publication, owned and operated by ophthalmologists, THE JOURNAL has become unique in the publishing industry. Its foreign circulation now nearly exceeds the total circulation in 1965, and is far greater than the circulation of many leading periodicals in medicine. Advertisers continue to view THE JOURNAL as a major voice in the market place. Authors favor THE JOURNAL with their best papers. A host of scientific referees and authors, a dedicated editorial board, and a first-class publication staff, headed by Mary L. Borysewicz, executive managing editor, assure the prompt monthly appearance of THE JOURNAL.

Much has been written about peer review since 1965. It is the ne plus ultra of a respected publication. I fully agree with Franz J. Ingelfinger,[2] late editor of the New England Journal of Medicine, who wrote:

> Editors who depend on referees to differentiate that which is publishable from that which is not, some would argue are a pusilanimous lot. If they do print an article which turns sour the mishap can be blamed on anonymous reviewers. Editors of course reject this mean spirited charge. But there is no doubt that the average editor, confronted by the products of today's rarified research, lacks the confidence to go it alone. He needs the help of the ultraspecialists to judge the ultraspecial articles so that his journal will print the best of what is submitted and will disseminate material that has the imprimatur of authority.

A major task of any editor is to select referees who will review articles in an unbiased, discerning, fair, objective manner. Mainly the system works well but there are slip-ups. We try to provide a timely review, and sometimes referees complain that the editorial office is unreasonable and peremptory in demanding that papers be returned before the referee has had time for full, mature consideration of the material. Rarely a referee uses pejorative language or provides a humorous review, and the editor must constructively and diplomatically revise the comments. Mainly, though, the reviews are of high quality. It is a pity that the opinion of a leading authority is known only to the editor and the authors of a paper, as the review often adds to our knowledge of a topic.

None of the many articles in the literature concerning peer review deal with the pre-publication review required by every publication. Many years ago, an experienced editor remarked that if a single-spaced article were submitted describing the definitive cure of cancer, he would reject it without review. One's critical sense becomes hardened when it is necessary to select the 15 to 20 papers that will appear each month from the 40 to 60 that have been considered.

Instructions to authors have been described as the more detailed the instructions the more prestigious the publication. It often seems, however, that the more detailed the instructions the less likely they are to be followed. When papers are submitted with single-spaced legends or references, or inadequate margins, one cannot help but wonder if any one of the many authors who have signed the copyright transfer and disclosure statement has even seen the typescript. THE JOURNAL is not a desktop publication, and I sigh when a paper is received that is decorated in a variety of type sizes, shapes, and fancy graphic touches.

Illustrations provide a particular problem. In every practice a whim of luck seems to dictate that the more interesting the abnormality the more likely the photographs are to be faulty. Such faulty pictures reproduce equally poorly on the printed page and serve only to confuse the reader. We dislike to reduce or enlarge illustrations, but the maximum size of the JOURNAL page is 6½ × 9 inches. Larger illustrations cannot be managed well.

Tables are expensive to prepare for printing and must be carefully reviewed. Sometimes authors will submit the working table used in the preparation of an article, which contains every iota of information about every patient.

We at THE JOURNAL make a major effort to publish material promptly. Papers are logged and assigned for review within 24 hours of receipt, and we aim to complete the review process within two weeks. Articles that pass the refereeing and pre-publication process are transferred to the computer by means of the Kurzweil Intelligent Scanning System, and thereafter only computer-generated copies are used. Authors' corrections are entered into the computer and the material is transferred to the familiar fonts of the printed page by a series of mnemonics. The film plates are transmitted to the printer, and some 14 weeks after the paper has been accepted it appears in THE JOURNAL.

My confidant and friend through these years at THE JOURNAL was David Shoch, who succeeded Herbert Haessler as editor of the abstract section in 1963, shortly after I was named associate editor. We became friends when I joined the staff at Northwestern Medical School where David was, at that time, a senior medical student and a frequent visitor to the Department of Biochemistry where he had received the Ph.D. degree. He turned to ophthalmology at the School of Aviation Medicine, then headed by General Victor A. Byrnes. On his return from military service, David disappointed a host of biochemists and internists at the Northwestern Hospitals when he enrolled in the graduate course in ophthalmology, which was initiated by Dr. Vail to assist military veterans. In 1953 Dr. Vail discontinued surgical ophthalmology after severe myocardial infarction, and Dr. Shoch became immediately involved in a large, demanding, international surgical practice with influential and prominent patients.

In more recent years, Drs. H. Stanley Thompson, Ronald Burde, Thomas Aaberg, and Michael Kass have met at the JOURNAL offices each month to consult concerning editorial matters. Dr. Thompson took over editorial direction of the book review section and more recently Dr. Kass succeeded Dr. Shoch as editor of the abstract section.

Mary L. Borysewicz joined THE JOURNAL in February 1973 as managing editor and has been in charge of all aspects of JOURNAL operation: subscriptions, advertising, marketing, editorial processing and production. As an independent publisher, The Ophthalmic Publishing Company manages all business and editorial matters without outside assistance. It is mainly the result of the efforts of Ms. Borysewicz and her staff that THE JOURNAL has become the major international publication in ophthalmology.

Since 1965, publication of THE JOURNAL has become far more complex. Circulation has doubled. The number of subscribers residing outside of the United States has exploded. English is not the primary language of many of the subscribers, and we make a major effort to provide text that all can understand.

THE JOURNAL changed slowly with the reduction in the length of the abstract section and the loss of the loyal collaborators who translated the abstracts to English from a host of languages. (Derrick Vail's first association with THE JOURNAL was as a collaborator to translate articles originally published in French.) The section on Notes, Cases, and Instruments has been replaced by the even more popular Letters to THE JOURNAL section. The News Items section is far more abbreviated. In January 1985, THE JOURNAL page dimensions were increased to their current size. THE JOURNAL nonetheless continues a two-column format, and Edward Jackson would easily recognize the publication he fathered in the third series.

The past three decades have been a golden era for me. There have been remarkable advances in nearly every phase of ophthalmology and in the practice of medicine. It has been a privilege to know so many of the leaders in ophthalmology throughout the world. I wish my successor an equally happy journey.

References

1. Newell, F. W.: Ophthalmology and the future. Arch. Ophthalmol. 74:448, 1965.
2. Ingelfinger, F. J.: Peer review in biomedical publications. Am. J. Med. 56:686, 1974.

Preoperative Medical Examinations for Patients Undergoing Ophthalmic Surgery

George B. Bartley and Bradly J. Narr

The setting for ophthalmic surgery varies from hospital operating rooms to ambulatory surgical centers to physicians' offices. The type of anesthesia likewise broadly ranges from general anesthesia for vitreoretinal, orbital, or pediatric surgery; to local anesthesia (often with sedation) for most anterior segment operations; to topical anesthesia for some minor procedures. Most ophthalmic surgery is elective and most patients are relatively healthy (Classes I or II) at the time of the operation, as defined by the American Society of Anesthesiologists (Table 1). Preoperative medical examinations and laboratory tests are often performed perfuncto-

TABLE 1
PHYSICAL STATUS CLASSIFICATION ESTABLISHED BY AMERICAN SOCIETY OF ANESTHESIOLOGISTS*

CLASS	DESCRIPTION
I	Healthy patient
II	Mild systemic disease, no functional limitation
III	Severe systemic disease, definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 hours with or without operation

*Reprinted by permission from Ross, A. F., and Tinker, J. H.: Anesthesia risk. In Miller, R. D. (ed.): Anesthesia, ed. 3, vol. 1. New York, Churchill Livingstone, Inc., 1990, pp. 715–742.

TABLE 2
MINIMAL PREOPERATIVE TEST REQUIREMENTS AT THE MAYO CLINIC*

AGE (YRS)	TESTS REQUIRED†
<40	None
40-59	Electrocardiography, measurement of serum creatinine and glucose
≥60	Complete blood cell count, electrocardiography, thoracic radiography, measurement of serum creatinine and glucose

*Modified from Narr, Hansen, and Warner.[6]

†The following additional guidelines apply: measurement of potassium is indicated in patients taking diuretics, thoracic radiography is indicated in patients with a history of cardiac or pulmonary disease or with recent respiratory symptoms, and a complete blood cell count is indicated in all patients who undergo blood typing and who are screened or cross-matched.

rily and generate considerable expense.[1] Their role and use have not been defined clearly in ophthalmic practice. We outline the guidelines for the preanesthetic medical examinations that have been developed at our institution for all surgical patients, including those undergoing ophthalmic procedures.

A healthy asymptomatic patient who is scheduled for a relatively minor procedure for which topical or local anesthetic will be used is not required to have medical testing in addition to an ophthalmic examination. If intravenous sedation is desired or general anesthesia is required, or if the surgeon is concerned about the patient's tolerance of the procedure (even if it only involves local anesthesia), a preanesthetic medical examination is conducted. All patients who undergo the specific operations of intraocular anterior segment surgery, vitreoretinal surgery, strabismus surgery, lacrimal drainage system surgery, or orbital surgery are examined preoperatively by an internist, anesthesiologist, or pediatrician.

The preoperative medical examination includes a review of the medical history and use of medications and a brief physical examination with particular attention paid to the cardiopulmonary system. The minimal preoperative laboratory test requirements vary according to the patient's age (Table 2). Because routine screening blood tests, electrocardiography, and thoracic radiography are not cost-effective and do not affect perioperative outcome, they are omitted for healthy patients younger than 40 years of age.[2-6] The preanesthetic medical examination is generally conducted a day or two before surgery, but is considered valid for adult patients if performed within six months before surgery and if there has been no remarkable illness in the interim. For pediatric patients, the examination must be conducted within one week before surgery for inpatient procedures and within one month before surgery for outpatient procedures.

Patients with debilitating cardiovascular or pulmonary disease, bleeding problems, uncontrolled blood glucose, uncontrolled hypertension, renal disease, hepatitis, jaundice, or substance abuse are ineligible for the preanesthetic medical examination and must undergo a more detailed general medical examination before anesthesia coverage is approved and surgery is performed.

The current guidelines at our institution have evolved over time and represent a consensus of anesthesiologists, surgeons, internists, and pediatricians. In our experience, they have been medically reasonable and cost-effective. Some ophthalmologists may be concerned that an undiagnosed cardiac dysrhythmia or other systemic disorder may pose a perioperative risk; but in asymptomatic patients, outcome has been shown to be unaffected by the elimination of many screening tests.[6] However, a careful history to elicit potential cardiovascular, respiratory, hematologic, or metabolic symptoms is important in identifying those patients who require a more detailed preoperative medical examination.

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References

1. Roizen, M. F., Kaplan, E. B., Schreider, B. D., Lichtor, L. J., and Orkin, F. K.: The relative roles of the history and physical examination, and laboratory testing in preoperative evaluation for outpatient surgery. The "Starling" curve of preoperative laboratory testing. Anesthesiol. Clin. North Am. 5:15, 1987.

2. Delahunt, B., and Turnbull, P. R. G.: How cost effective are routine preoperative investigations? N.Z. Med. J. 92:431, 1980.

3. Wood, R. A., and Hoekelman, R. A.: Value of the chest x-ray as a screening test for elective surgery in children. Pediatrics 67:447, 1981.

4. Rabkin, S. W., and Horne, J. M.: Preoperative electrocardiography. Effect of new abnormalities on clinical decisions. Can. Med. Assoc. J. 128:146, 1983.

5. O'Connor, M. E., and Drasner, K.: Preoperative laboratory testing of children undergoing elective surgery. Anesth. Analg. 70:176, 1990.

6. Narr, B. J., Hansen, T. R., and Warner, M. A.: Preoperative laboratory screening in healthy Mayo patients. Cost-effective elimination of tests and unchanged outcomes. Mayo Clin. Proc. 66:155, 1991.

LETTERS TO THE JOURNAL

Phialophora mutabilis Keratomycosis

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Phialophora (*Lecythophora*) *mutabilis* is a dematiaceous fungus that is commonly found in soil and wood. These fungi are an uncommon cause of keratitis.

A 36-year-old man, referred to one of us (K.A.M.) in September 1990, had a corneal abscess in his left eye. In March 1990, concrete from a brick wall had hit his left eye and caused a corneal laceration. Concrete particles were removed at the patient's local hospital. He had no further problems until three weeks before being seen when he felt some irritation in his left eye. A corneal infiltrate was observed by a local ophthalmologist who prescribed tobramycin eyedrops. The patient was referred when the keratitis did not improve.

At examination, the visual acuity was 20/15 unaided in each eye. There was an abscess in the inferior paracentral portion of the left cornea in the depth of an old shelving scar, and hyphae extended from this abscess into the anterior chamber (Fig. 1). A corneal biopsy was performed under general anesthesia and specimens were obtained for culture. Postoperatively, natamycin 5% was administered topically every hour. On day 7, because of lack of response to treatment, nystatin 1% was added hourly. A penetrating keratoplasty was performed three days later when the abscess became more dense and the visual acuity decreased to 20/200. Treatment was continued

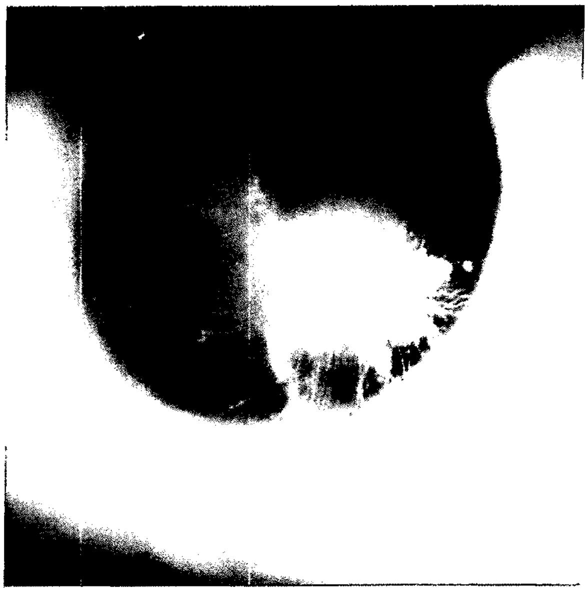

Fig. 1 (Ho, Bernard, and McClellan). The left cornea shows an infiltrate with feathery margins.

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped or reducible to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

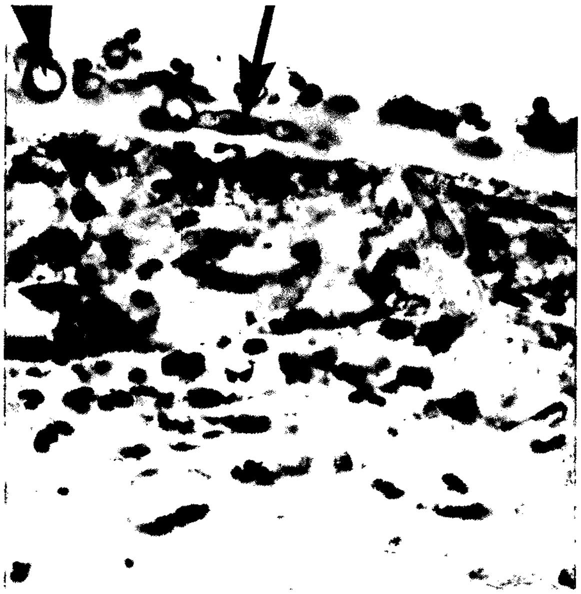

Fig. 2 (Ho, Bernard, and McClellan). Histologic section of the deep portion of the corneal button (posterior surface uppermost) shows a dense cellular infiltrate and fungal hyphae penetrating Descemet's membrane (arrow) to spread on the endothelial surface (arrowhead).

with ketoconazole, 200 mg orally twice a day. One colony of fungus had grown from cultures after three days. In vitro sensitivity testing (National Medical Mycological Reference Laboratory, Royal North Shore Hospital, Sydney) showed the isolated fungus to be resistant to amphotericin B, flucytosine, and itraconazole but sensitive to ketoconazole. The fungus was identified as *P. mutabilis van Beyma* by the International Mycological Institute, London. The corneal graft has remained clear with no fungal recurrence for a follow-up period of 12 months.

Histopathologic examination of the corneal button showed a deep fungal abscess with hyphae penetrating Descemet's membrane to spread on the posterior surface of the cornea (Fig. 2).

Previous reports of *Phialophora* keratomycosis are rare.[1-3] Like most cases of keratomycosis, the infection in our patient occurred after outdoor corneal trauma.[4] Since the infiltrate was in the depths of the corneal scar, we believe that the organism was inoculated into the cornea at the time of the injury in March 1990. The six-month interval between the trauma and the clinical infection probably reflects the low virulence and the opportunistic nature of the organism.

This case demonstrates some of the problems in the treatment of keratomycosis. After making a presumptive diagnosis, the choice of antifungal agents is difficult because identification and sensitivity testing often involve significant delay. In our case, topical natamycin therapy was selected initially because of its wide spectrum of activity.[5] The lack of improvement then prompted addition of nystatin topically. Despite treatment, clinical progression of the infection necessitated keratoplasty.

References

1. Wilson, L. A., Sexton, R. R., and Ahearn, D.: Keratochromomycosis. Arch. Ophthalmol. 76:811, 1966.
2. Polack, F. M., Siverio, C., and Bresky, R. H.: Corneal chromomycosis. Double infection by *Phialophora verrucosa* Medlar and *Cladosporium cladosporioides* Frescenius. Ann. Ophthalmol. 8:139, 1976.
3. Eiferman, R. A., Snyder, J. W., and Barbee, J. V.: Corneal chromomycosis. Am. J. Ophthalmol. 95:255, 1983.
4. Forster, R. K., Rebell, G., and Wilson, L. A.: Dematiaceous Fungal keratitis. Br. J. Ophthalmol. 59:372, 1975.
5. Forster, R. K., and Rebell, G.: The diagnosis and management of keratomycosis. II Medical and surgical management. Arch. Ophthalmol. 93:1134, 1975.

Keratoconus Associated With Posterior Polymorphous Dystrophy

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A 31-year-old Hispanic man who had complained of deteriorating vision in his left eye for the past two years was examined at our institution. He had a 15-year history of a corneal dystrophy in both eyes. His mother and a cousin were reported to have a similar ocular disor-

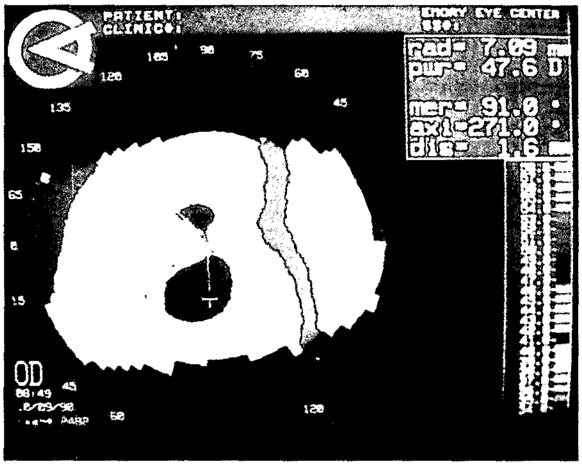

Fig. 1 (Bechara and associates). Computer-assisted videokeratography of the right cornea shows signs suggestive of early keratoconus including an asymmetric astigmatic pattern, much steeper inferiorly with a slight displacement.

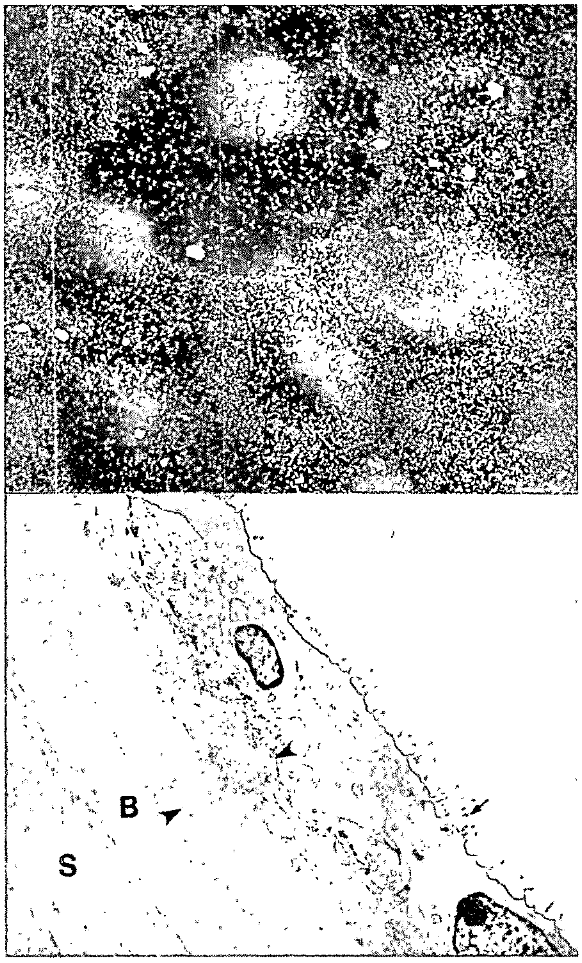

Fig. 2 (Bechara and associates). Top, Numerous microvillus processes project from the posterior endothelial surface (× 1,600). Bottom, Multilayered endothelium with numerous microvillus processes overlies fibrillar posterior collagenous layer and banded posterior collagenous layers (between arrowheads) that are posterior to the fetal banded (B) portion of Descemet's membrane and the stroma (S) (× 8,700).

der; however, they were unavailable for examination. His spectacle best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/300. Slit-lamp microscopy disclosed bilateral geographic and band-shaped lesions at the level of a translucent Descemet's membrane, consistent with a diagnosis of posterior polymorphous dystrophy. Although there was no evidence on slit-lamp examination of keratoconus, computer-assisted keratography of his right eye showed a nonlinear, assymetrical bow-tie astigmatic pattern[1] (Fig. 1), with greater steepening of the inferior cornea compared with the superior cornea, and a slight temporal displacement of both inferior and superior areas of the steepening, all of these features consistent with early keratoconus.[2] The corneal stroma in his left eye was diffusely edematous and some epithelial bullae were present, precluding keratometry and keratography. The corneal thickness was 0.560 μm in his right eye and 0.700 μm in his left eye. Results of the remainder of the ophthalmic examination were unremarkable. A penetrating keratoplasty was performed in his left eye.

Histopathologic examination of the corneal button showed that the epithelium and Bowman's layer were focally disrupted; the stroma was thickened and edematous peripherally and thinned centrally; Descemet's membrane was intact; and some endothelial cells were multilayered. Examination by scanning and transmission electron microscopy showed numerous microvillus processes on the posterior surface of multilayered endothelium overlying a posterior collagenous layer composed of fibrillar material (Fig. 2). The diagnosis was keratoconus and posterior polymorphous dystrophy.

Keratoconus may be thought of as a sign, like corneal edema, and not a specific diagnostic entity. Keratoconus may be associated with systemic diseases such as atopy, may be familial, or may occur as an isolated ocular abnormality.[3] Gasset and Zimmerman[4] described two patients, a 32-year-old man and a 50-year-old woman, with associated keratoconus and posterior polymorphous dystropy. Weissman and associates' report[5] included four cases, all occurring in young men. All previously reported cases showed clearly established keratoconus and posterior polymorphous dystrophy. In our case, the posterior polymorphous dystrophy was fully established; there were only early videokeratographic clinical signs suggestive of keratoconus[2] in the right eye. Keratometry was masked in the left eye by the surface irregularities secondary to epithelial bullae. The histopathologic findings of the corneal button were consistent with the diagnosis of keratoconus and posterior polymorphous dystrophy.

References

1. Bogan, S. J., Waring, G. O. III, Ibraham, O., Drews, C., and Curtis, L.: Classification of normal corneal topography based on computer-assisted videokeratography. Arch. Ophthalmol. 108:945, 1990.
2. Rabinowitz, Y. S., Garbus, J., and McDonnell, P. J.: Computer-assisted corneal topography in family members of patients with keratoconus. Arch. Ophthalmol. 108:365, 1990.
3. Krachmer, J. H., Feder, R. S., and Belin, M. W.: Keratoconus and related noninflammatory corneal thinning disorders. Surv. Ophthalmol. 28:293, 1984.
4. Gasset, A. R., and Zimmerman, T. J.: Posterior polymorphous dystrophy associated with keratoconus. Am. J. Ophthalmol. 78:535, 1974.
5. Weissman, B. A., Ehrlich, M., Levenson, J. E., and Pettit, T. H.: Four cases of keratoconus and posterior polymorphous corneal dystrophy. Optom. Vis. Sci. 66:243, 1989.

A Disposable Iris Retractor for Vitrectomy

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A small pupil makes vitrectomy difficult and can be managed by traditional sphincterotomy. However, temporary enlargement of the pupil is preferable for cosmesis, function, and to prevent the migration of silicone oil into the anterior chamber. Suture fixation of the iris[1] and mechanical iris retractors[2-4] have been developed to allow temporary enlargement of the pupil. Mechanical iris retraction takes less time than sutures. However, previously described mechanical retractors are either specialized proprietary products or are made of materials that are not readily available in the operating room.

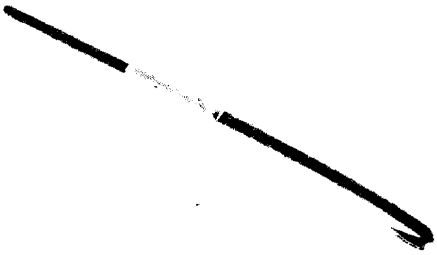

Fig. 1 (Chong). The iris retractor consists of a 30-gauge, disposable, beveled needle and a 32-style silicone strip.

This iris retractor is made of a disposable 30-gauge beveled needle and a 32-style silicone strip (Fig. 1). The beveled tip of the 30-gauge needle is passed through a small piece of the silicone strip. The beveled tip of the needle is bent to an acute angle with needle holders. The needle is then broken off at the plastic hub. The iris retractor is placed through microvitreoretinal blade incisions, which are sharply beveled so they can be self sealing. The pupil is engaged and the silicone strip is snugged against the corneoscleral limbus for countertraction (Fig. 2).

These iris retractors are quickly made in the operating room in quantity from materials

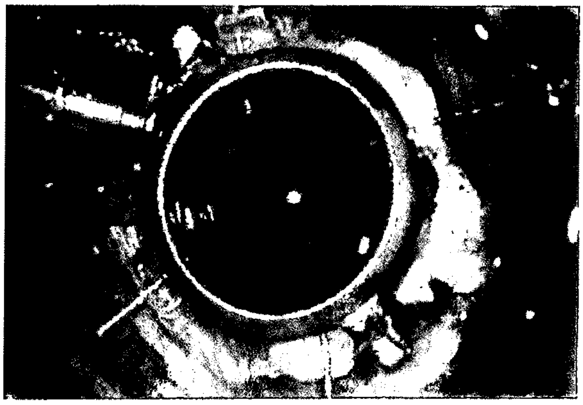

Fig. 2 (Chong). The pupil has been widely stretched with four disposable iris retractors.

readily available in any vitrectomy suite. They are disposed after each case. With proper angulation of the 30-gauge needle tip, there is no problem in withdrawing the 30-gauge needle through the limbal incision.

References

1. Eckardt, C.: Pupillary stretching. A new procedure in vitreous surgery. Retina 5:235, 1985.
2. Madeira, D., and Stern, W. H.: Iris suture hook for pupillary dilation in vitreoretinal surgery. Am. J. Ophthalmol. 106:743, 1988.
3. McCuen, B., Hickingbotham, D., Tsai, M., and de Juan, E., Jr.: Temporary iris fixation with a micro-iris retractor. Arch. Ophthalmol. 107:925, 1989.
4. Fuller, D. G., and Wilson, D. L.: Translimbal iris hook for pupillary dilation during vitreous surgery. Am. J. Ophthalmol. 110:577, 1990.

A Comparison of Three Contact-Lens Biomicroscopy Coupling Solutions

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Contact-lens biomicroscopy is often avoided before diagnostic photography because of the concern that corneal clarity could be disturbed by the contact lens or the viscous coupling solution used for the examination. Examples of such highly viscous solutions are carboxyethylcellulose (Gonioscopic, Alcon, Fort Worth, Texas) and 2.5% hydroxypropyl methylcellulose (Goniosol, Iolab Corp., Claremont, California). Balanced saline solution[1,2] and 1% carboxymethylcellulose[3] (Celluvisc, Allergan Pharmaceuticals, Irvine, California) have been recommended as alternatives to these highly viscous solutions to avoid the theoretical disadvantage of disturbed corneal clarity. Additionally, these two media contain no preservatives that might irritate the corneal epithelium, and they do not require irrigation, thus aiding more rapid return of visual function. One potential disadvantage to the use of saline or carboxymethylcellulose for biomicroscopy is less mechanical protection to the corneal epithelium than with the more viscous methylcellulose preparations.[3] Additionally, the low viscosity of saline provides only a weak bond between the cornea and contact lens, which results in possible bubble formation under the lens.

We sought to determine which coupling solution was optimal for fundus photography after contact-lens biomicroscopy. Forty-five consecutive eyes undergoing macular photocoagulation were randomly assigned into one of three groups based on the coupling agent used for treatment: Group 1, balanced saline solution; Group 2, 1% carboxymethylcellulose; or Group 3, 2.5% hydroxypropyl methylcellulose. All eyes were treated with topical anesthetic drops and the Mainster lens. The laser surgeon (R.J.O.) was unaware of the coupling solution used for each case. Of the 45 eyes treated, 30 had diabetic macular edema, ten had subretinal neovascular membranes, and five had vein occlusion. Within 30 minutes of treatment, posttreatment stereoscopic fundus photography was performed. An independent masked comparison of pretreatment and immediate posttreatment stereoscopic fundus photographs was made by each of us.

On comparison of pre- and posttreatment photographic clarity for the 45 eyes, no marked difference was found among the three groups of coupling solutions. In 13 eyes treated with saline as the coupling agent, posttreatment clarity was the same in ten eyes (77%) and worse in three (23%). In 15 eyes treated with carboxymethylcellulose 1%, posttreatment clarity was the same in 12 eyes (80%) and worse in three eyes (20%). In 17 eyes treated with hydroxypropylmethylcellulose 2.5%, 13 eyes (76%) had the same posttreatment clarity and four (24%) had worse clarity. We agreed on 41 of the 45 case comparisons initially, and agreement was readily reached after a second review of the other four cases. In no case was the clarity between the pre- and posttreatment photograph pairs believed to be of clinical importance.

From these data, we concluded that balanced saline solution, 1% carboxymethylcellulose, and 2.5% hydroxypropyl methylcellulose are comparable as contact-lens biomicroscopy coupling solutions. No one solution is optimal for fundus photography after biomicroscopy, and posttreatment fundus photographs were just as clear as pretreatment photographs, regardless of which coupling agent was used.

References

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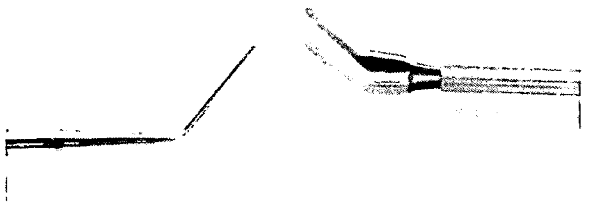

Fig. 1 (Thomas and associates). Angled subretinal pick (left) and horizontal subretinal forceps (right).

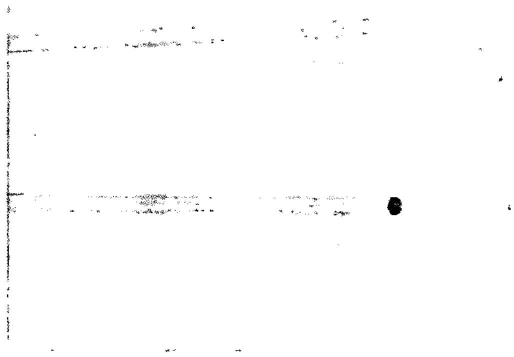

Fig. 2 (Thomas and associates). Thirty-gauge infusion needles: angled (above), and straight (below).

We have developed instruments that greatly facilitate this surgery as well as the removal of submacular hematomas.[2-5]

The angled pick (Fig. 1) has a 20-gauge shaft, a 130-degree bend, and a flattened tip tapering to 0.305 mm. The pick can be used to dissect gently under the neovascular complex in the presumed ocular histoplasmosis syndrome. The blade can be used to push against and break the neovascular connecting stalk.

The 20-gauge needle tapers to 30-gauge proximal to the 130-degree angle. The blunt 30-gauge tip measures 3.2 mm in length. A syringe filled with balanced salt solution is connected via a short piece of intravenous tubing to the hand piece and allows gentle infusion through the retinotomy. The angle of the tip allows direction of the infusion toward the subfoveal space as opposed to refluxing into the vitreous cavity.

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We have used these instruments in more than 20 cases of subfoveal surgery and find them helpful.

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When the patient was seen one week later, the best-corrected visual acuity in the right eye had improved to 20/40. The retinal hemorrhage had disappeared, and the vitreous was clear, except for a few resolving blood clots inferiorly. The retina was normal. The sequence of events and the lack of other contributing factors suggest that the intraocular hemorrhage was secondary to the intravenous administration of streptokinase.

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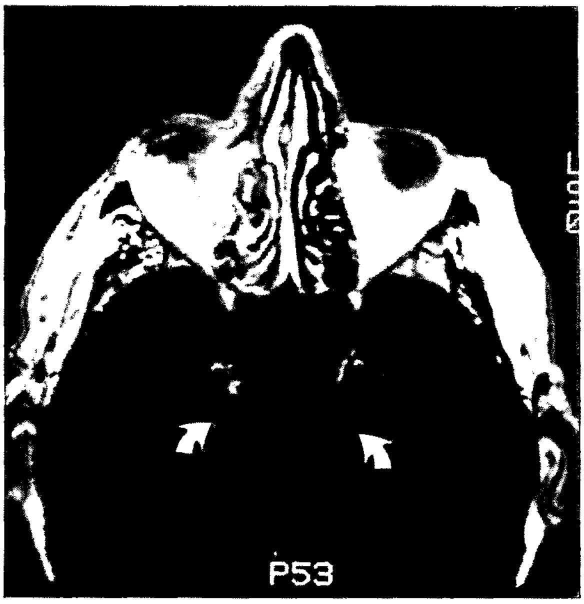
A 64-year-old man was seen on referral after oral treatment with acyclovir for herpes zoster ophthalmicus in the right eye. Sequentially, the patient developed blepharoptosis, corneal hypesthesia, and anterior uveitis in the right eye, which cleared with topical corticosteroid therapy. The patient was referred one month later when the uveitis recurred in the right eye, and uveitis developed in the left eye. The patient now had ophthalmoplegia in the right eye, bilateral corneal hypesthesia, vitreous inflammation, greater in the left than the right, and a large area of acute retinal necrosis superiorly in the left eye.

The anterior uveitis responded to topical corticosteroid therapy, and the peripheral retina in the left eye received 360 degrees of krypton laser photocoagulation posterior to the areas of retinal necrosis. The patient was hospitalized and received acyclovir intravenously, 1,300 mg



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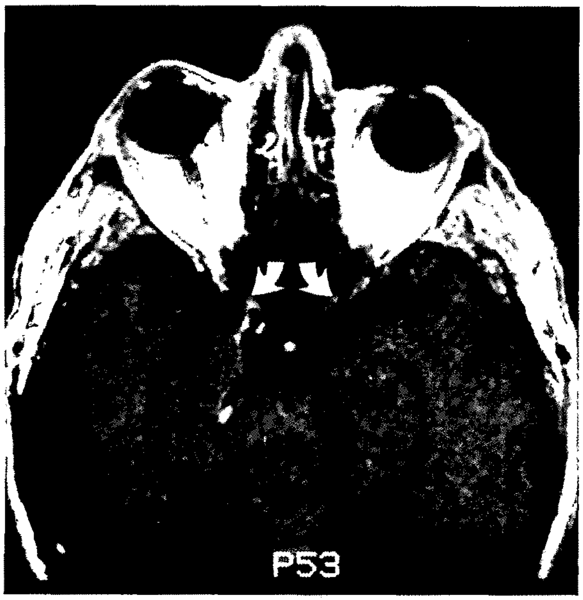

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every six hours and prednisone, 80 mg orally per day. Tests for toxoplasmosis, syphilis, cytomegalovirus, and herpes simplex were negative. A varicella-zoster virus antibody immunoassay was 1:512. Magnetic resonance imaging disclosed abnormal enhancement of the optic nerves, chiasm, and both trigeminal nerve roots, greater in the right than the left (Figs. 1 and 2).

The patient's ocular condition stabilized. Visual acuity was R.E.: 20/100 and L.E.: 20/200, and he was discharged after completing a 14-day course of intravenously administered acyclovir.

One month later the patient was re-hospitalized because the visual acuity in his left eye had deteriorated to bare light perception. New findings of optic disk pallor in the left eye with pigmentation in the area of acute retinal necrosis but no retinal detachment were observed. Repeat magnetic resonance imaging disclosed an occluded left internal carotid artery, resolution of the trigeminal nerve enhancement, and an abnormal signal of the right parahippocampal gyrus on T_2-weighted image. He again received acyclovir intravenously and methylprednisolone. At discharge the visual acuity in the left eye was still light perception.

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4. Jabs, D. A., Schachat, A. P., Liss, R., Knox, D. L., and Michels, R. G.: Presumed varicella zoster retinitis in immunocompromised patients. Retina 7:9, 1987.

5. Bosem, M. E., Harris, R., and Atherton, S. S.: Optic nerve involvement in viral spread in herpes simplex virus type I retinitis. Invest. Ophthalmol. Vis. Sci. 31:1683, 1990.

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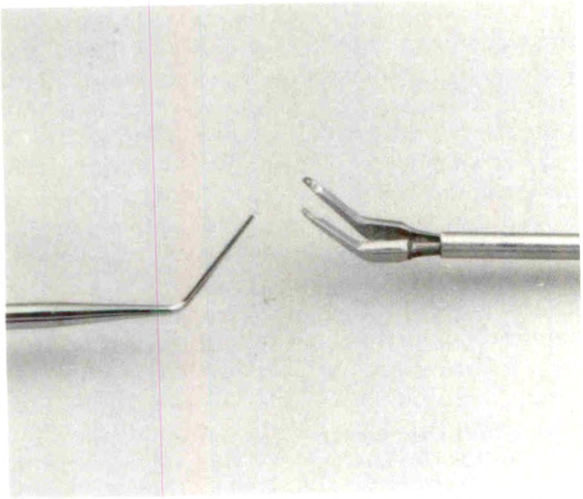

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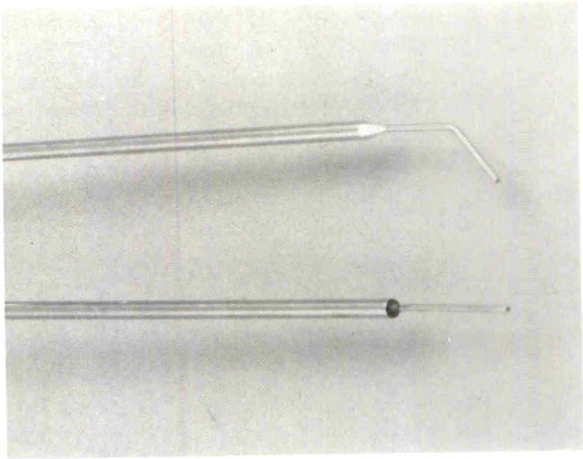

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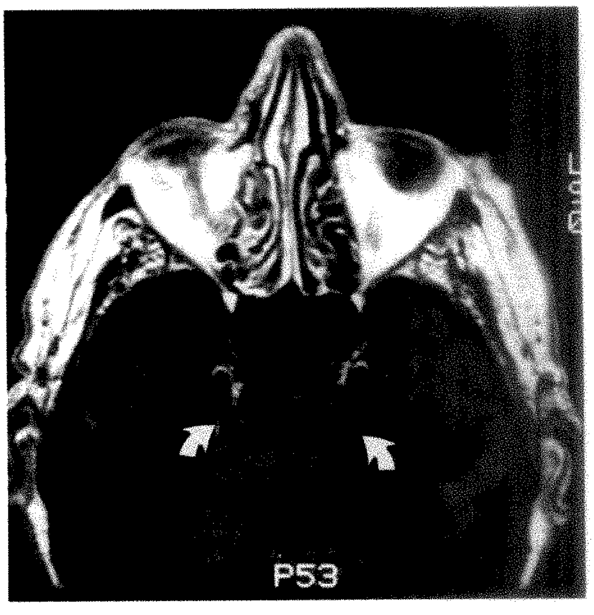

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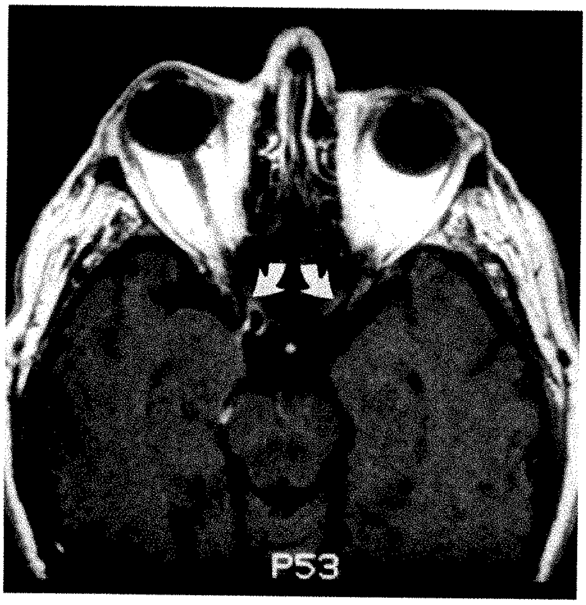

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2. Schwartz, J. N., Cashwell, F., Hawkins, H. K., and Klintworth, G. K.: Necrotizing retinopathy with herpes zoster. Arch. Pathol. Lab. Med. 100:386, 1976.

3. Browning, D. J., Blumenkrantz, M. S., Culbertson, W. W., Clarkson, J. D., Tardif, Y., Gourdeau, A., and Minturn, J.: Association of varicella zoster dermatitis with acute retinal necrosis syndrome. Ophthalmology 94:602, 1987.

4. Jabs, D. A., Schachat, A. P., Liss, R., Knox, D. L., and Michels, R. G.: Presumed varicella zoster retinitis in immunocompromised patients. Retina 7:9, 1987.

5. Bosem, M. E., Harris, R., and Atherton, S. S.: Optic nerve involvement in viral spread in herpes simplex virus type I retinitis. Invest. Ophthalmol. Vis. Sci. 31:1683, 1990.

Metronidazole and Optic Neuritis

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and Mike Dreis, R.Ph.

National Registry of Drug-Induced Ocular Side Effects, Casey Eye Institute, Oregon Health Sciences University (D.P., F.T.F.); and Division of Drug Experience, Food and Drug Administration (M.D.). This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York.

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Metronidazole (Flagyl, Metric 21, Protostat) is used in the treatment of trichomoniasis, amebiasis, giardiasis, and anaerobic bacterial infections. Ocular side effects from systemic use of metronidazole are uncommon and reversible after discontinuation of the drug. Ocular side effects associated with metronidazole include decreased vision, photophobia, ocular allergic reactions, visual hallucinations, oculogyric crises, diplopia, and subconjunctival or retinal hemorrhages secondary to drug-induced anemia.[1] There has been one report of ocular abnormalities in an infant after maternal use of this agent during the first trimester.[2]

The National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon) and the Federal Drug Administration Spontaneous Reporting System have received seven case reports of retrobulbar or optic neuritis associated with the oral use of metronidazole. Optic neuritis or retrobulbar neuritis were not unlike those reported with other drugs. Abnormalities include color vision defects, decreased vision, and various scotomas. Dosage of the drug varied from 750 mg to 1 g daily. Length of time on the drug varied from seven to 365 days; the age group ranged from 26 to 53 years, with four women and three males. Four of the patients had bilateral optic nerve involvement and two were also taking butalbital or sulfasalazine, which have also been associated with optic neuritis.[1] Most patients recovered normal vision, although two had some residual deficit. Peripheral neuropathy was seen in two of these patients.

A number of reports have implicated metronidazole as a cause of peripheral neuropathy.[3] Sensory neuropathy, in a "stocking glove" distribution, is the most characteristic finding. In one study, 11 of 13 patients treated with metronidazole for Crohn's disease developed sensory peripheral neuropathy, demonstrated either by decreased nerve conduction velocities or abnormal results of neurologic examination.[4] Therefore, this agent can affect the neurologic system. A cause-and-effect relationship between metronidazole and optic nerve disease is not definitive, in part, because none of these patients were rechallanged. An additional problem involves distinguishing this form of optic nerve disease from symptoms of multiple sclerosis. In one case, the physician suspected multiple sclerosis because of associated paresthesias. However, optic neuritis with peripheral neuropathy is unusual in multiple sclerosis patients.[5]

The reason for this report is that this is a large number of cases in proportion to any other drug that we have been following in the Registry involving optic neuritis and retrobulbar neuritis associated with a drug. Although we cannot prove a cause-and-effect relationship, we believe there have been enough cases reported to place this drug on the "suspect" list, and metronidazole needs to be considered as a possible cause when unexplained optic nerve disease develops.

References

1. Fraunfelder, F. T.: Drug-Induced Ocular Side Effects and Drug Interactions, ed. 3. Philadelphia, Lea & Febiger, Philadelphia, 1989, pp. 65–66.
2. Cantu, J. M., and Garcia-Cruz, D.: Midline facial defect as a teratogenic effect of metronidazole. Birth Defects 18:85, 1982.
3. Snavely, S., and Hodges, G.: The neurotoxicity of antibacterial agents. Ann. Intern. Med. 101:92, 1984.
4. Duffy, L., Daum, F., Fisher, S., Selman, J., Vishnubhakat, S., Aiges, H., Markowitz, J., and Silverberg, M.: Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 88:681, 1985.
5. Wartenberg, R.: Neuritis and multiple sclerosis. In Neuritis, Sensory Neuritis, Neuralgia. A Clinical Study With Review of the Literature. New York, Oxford University Press, pp. 296–305, 1958.

Extreme Corneal Flattening After Radial Keratotomy

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and S. Lance Forstot, M.D.
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Progressive flattening of the cornea after radial keratotomy has been well documented.[1] The final extent of this flattening has not been determined.[2] In our corneal and refractive referral practice, we have seen patients who have continued postoperatively to have corneal flattening, approximately 1.0 diopter per year for up to ten years. This flattening results in Humphrey automated keratometry readings below 30.0 diopters in one primary meridian.

A 45-year-old woman underwent bilateral eight-incision radial keratotomies elsewhere in 1984. Preoperative, cycloplegic, manifest refraction was R.E.: −5.75 + 1.00 × 85 degrees and L.E.: −6.00 + 0.50 × 65 degrees. Preoperative keratometry readings were R.E.: 41.00/42.37 × 86 degrees and L.E.: 41.25/42.37 × 80 degrees.

Eight-incision radial keratotomies with an optical zone of 3.5 mm without re-deepening were performed with a diamond knife in 1984. One year postoperatively, the patient's visual acuity without correction was R.E.: 20/20 and L.E.: 20/25 +1. Keratometry readings were R.E.: 37.00/38.75 × 85 degrees and L.E.: 36.25/35.87 × 113 degrees. The cycloplegic, manifest refraction was R.E.: −0.50 + 0.50 × 90 degrees and L.E.: +0.25 + 0.75 × 165 degrees.

During the next seven years, the corneas gradually flattened and, on April 24, 1989, keratometry readings were R.E.: 35.25/36.25 × 68 degrees and L.E.: 33.87/29.00 × 91 degrees. Cycloplegic, manifest refraction was R.E.: +2.50 + 0.50 × 155 degrees and L.E.: +5.25 + 2.25 × 167 degrees. Uncorrected visual acuity was R.E.: 20/30 and L.E.: 20/100. Corrected visual acuity was 20/20 in both eyes.

A 43-year-old man had an initial, cycloplegic, manifest refraction of R.E.: −9.75 + 0.75 × 105 degrees with 20/30 visual acuity and L.E.: −10.25 + 0.50 × 75 degrees with 20/30 visual acuity. Keratometry readings were R.E.: 43.00/43.87 and L.E.: 43.37/44.37.

In 1980, one of us (R.E.D.) performed bilateral 16-incision radial keratotomies with 3-mm optical zones and peripheral re-deepenings by using a diamond blade.

One year postoperatively, visual acuity without correction was R.E.: 20/60 +1 and L.E.: 20/40 +1. Keratometry readings were R.E.: 34.87/31.25 × 103 degrees and L.E.: 34.37/30.12 × 87 degrees. A manifest refraction was R.E.: +0.50 + 2.25 × 5 degrees and L.E.: plano +1.25 × 154 degrees.

Ten years postoperatively, keratometry readings were 32.75/29.25 × 123 degrees and L.E.: 32.25/27.75 × 97 degrees. Cycloplegic, manifest refraction was R.E.: +4.00 + 6.00 × 15 degrees and L.E.: +4.50 + 4.00 × 155 degrees. Visual acuity in each eye without correction was 20/200 and, with correction, 20/30.

It appears that after eight- and 16-incision radial keratotomies for severe myopia, corneas may continue to flatten dramatically over the ensuing years. Using the Humphrey automated keratometer, it is possible to document this excessive flattening. These measurements are obviously well beyond the range of the conventional Haag-Streit and Bausch & Lomb keratometers. The readings taken with the automated keratometer are not exactly comparable to the readings taken with conventional keratometers using additional lenses. However, in conjunction with the documented progression of the hyperopia, it is clear that in these two cases, progression of the corneal flattening reached levels not previously documented.[3]

References

1. Dietz, M. R., Sanders, D. R., and Raanan, M. G.: Progressive hyperopia in radial keratotomy. Long-term follow-up of diamond knife and metal blade series. Ophthalmology 93:1284, 1986.
2. Waring, G. O., Lynn, M. J., Fielding, B., Asbell, P. A., Balyeat, H. D., Cohen, E. A., Culbertson, W., Doughman, D. J., Fecko, P., McDonald, M. B., and the PERK Study Group: Results of the prospective evaluation of radial keratotomy (PERK) study four years after surgery for myopia. JAMA 263:1083, 1990.
3. Barraquer, J.: Radial keratotomy. Refractive surgery. In Jaffe, N. (ed.): Atlas of Ophthalmic Surgery, Chap. 7. Philadelphia, J. B. Lippincott, 1990, p. 7.6.

Isolated Orbital Sarcoidosis as a Cause for Blepharoptosis

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A 65-year-old white woman developed blepharoptosis of the right upper eyelid over a six-month period without pain, diplopia, or constitutional symptoms. Her palpebral fissure width measured 5 mm on the right and 8 mm on the left with 15 mm of levator palpebrae superioris muscle function bilaterally. No exophthalmos or palpable mass was present. Visual acuity was correctable to 20/25 in both eyes. Ocular movements were normal. No pupillary abnormalities were noted. Slit-lamp examination disclosed normal conjunctiva, cornea, and anterior chamber. Results of bilateral ophthalmoscopy were unremarkable.

The patient's blepharoptosis was treated successfully by a Fasanella-Servat procedure. After ten months, the blepharoptosis recurred. Results of thyroid function studies were normal as was a complete blood cell count. The serum angiotensin-converting enzyme level was normal. Results of edrophonium chloride testing were negative. A chest x-ray film was normal. A computed tomographic scan of the orbit showed enlargement of the right superior rectus-levator palpebrae superioris muscle complex (Figure). Histopathologic examination of a biopsy specimen of the levator palpebrae superioris muscle showed noncaseating granulomas and was negative for acid-fast bacilli and fungi.

She was treated with oral prednisone, 40 mg daily, which relieved her blepharoptosis. However, when the prednisone was discontinued, the blepharoptosis recurred and a palpable mass developed in the affected eyelid. Biopsy of this mass two months after the initial biopsy also showed noncaseating granulomas consistent with sarcoidosis. Cultures were negative for acid-fast bacilli and fungi. A concurrent angiotensin converting enzyme level was 91 units/l (normal < 55 units/l). The patient currently receives 40 mg of prednisone and 50,000 units of vitamin D daily, as well as calcium supplementation.

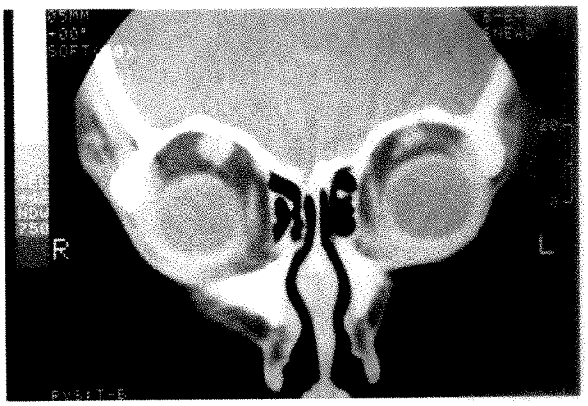

Figure (Snead and associates). Computed tomographic scan (coronal section) demonstrating enlargement of the right superior rectus-levator muscle complex.

Sarcoidosis is a disease of unknown origin, which causes chronic noncaseating granuloma formation. Between 7% and 15% of cases present with eye symptoms or signs.[1] These can include uveitis, conjunctival granulomas, retinal periphlebitis, choroidal nodules, chorioretinitis, papilledema, Heerfordt's syndrome (uveitis, parotitis, fever, and facial paralysis), or orbital tumors.[2] Sarcoidosis occurs more frequently in blacks and in women. Orbital involvement is often in the lacrimal gland and may manifest as an eyelid mass.[3] Our case of primary orbital sarcoidosis is unusual in two respects in that it occurred in a white woman and did not manifest as an eyelid or orbital mass but as blepharoptosis caused by involvement of the levator palpebrae superioris muscle.

References

1. Sacher, M., Lanzieri, C. F., Sobel, L. I., and Som, P. M.: Computed tomography of bilateral lacrimal gland sarcoidosis. J. Comput. Assist. Tomography 8:213, 1984.
2. Leino, M., Tuovinen, E., and Romppanen, T.: Orbital sarcoidosis. A case report. Acta Ophthalmologica 60:809, 1982.

3. Imes, R. K., Reifschneider, J. S., and O'Connor, L. E.: Systemic sarcoidosis presenting initially with bilateral orbital and upper lid masses. Ann. Ophthalmol. 20:466, 1988.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Echographic Diagnosis of Dural-Carotid Cavernous Sinus Fistulas

EDITOR:

I read with interest the article, "Echographic diagnosis of dural carotid-cavernous sinus fistulas" by R. H. Spector (Am. J. Ophthalmol. 111:77, January 1991). It is always refreshing to read articles supporting the use of standardized echography in the evaluation of orbital disorders, including carotid-cavernous and indirect (dural) arteriovenous fistulas. I take issue, however, with the presentation of A-scan values for normal extraocular muscles on page 78 of the article. These unreferenced values originated from the Bascom Palmer Eye Institute Echography Department. Furthermore, the author did not obtain permission to use these data, derived from an incomplete study of 26 normal subjects. The study has now been completed, 38 subjects having been measured. This current study is an update of work published by McNutt, Kaefring (Frazier Byrne) and Ossoinig[1] in 1977. Since that time, several studies have been published that describe the combined use of B- and standardized A-scan for extraocular muscle evaluation.[2-4] Our present study utilized these combined techniques with improved instrumentation for better resolution and more precise electronic measurements.

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References

1. McNutt, L. C., Kaefring S. L., and Ossoinig, K. C.: Echographic measurement of extraocular muscles. In White, D., and Brown, R. E. (eds.): Ultrasound in Medicine, vol. 3A. Basel, Karger, 1977, pp. 927–932.
2. Ossoinig, K. C.: Standardized echography. Basic principles, clinical applications and results. Int. Ophthalmol. Clin. 19:165, 1979.
3. Byrne, S. F.: Standardized echography of the eye and orbit. Neuroradiology 28:618, 1986.
4. Byrne, S. F., and Glaser, J. S.: Orbital tissue differentiation with standardized echography. Ophthalmology 90:1071, 1983.

Reply

EDITOR:

The A-scan values for normal extraocular muscles that appeared in my article were given to me in 1987 by the Director of Echography at Bascom Palmer Eye Institute. The values were also pinned to the bulletin boards of each examination room in Bascom Palmer Eye Institute's Department of Echography. I assumed the values to be time-tested, accurate, and statistically sound for two reasons: not a single amendment had made to them over a three-year period, from 1987 to 1990, when I visited the echography department; and each of the Bascom Palmer Eye Institute echographers routinely referred to these values in their day-to-day echographic examinations of patients with suspected enlargement of the extraocular muscles.

Throughout the performance of my study and the preparation of my manuscript I used the extraocular muscle measurements in the same way I saw them used at Bascom Palmer Eye Institute. There was no intent to take credit for the investigative work that went into ascertaining these data. They were accumulated by the members of the department of echography at Bascom Palmer Eye Institute, and I commend them for their final results.

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Optic Nerve Sheath Decompression for the Treatment of Progressive Nonarteritic Ischemic Optic Neuropathy

EDITOR:

The article, "Optic nerve sheath decompression for the treatment of progressive nonarteritic ischemic optic neuropathy" by T. C. Spoor, M. J. Wilkinson, and J. M. Ramocki (Am. J. Ophthalmol. 111:724, June 1991), leaves several important questions unaddressed. Were the cases consecutive or selected? How many cases of anterior ischemic optic neuropathy were diagnosed during the study period? How many of these cases were followed up to see if they would progress? What happened to eyes with progressive anterior ischemic optic neuropathy that were not operated on? Were visual acuity measurements done by the same examiners using the same techniques? Visual acuity measurements may vary widely between examinations when there is a central defect with a sharp border close to fixation.[1] As assessment of visual acuity and visual field is inherently subjective, why not use an objective method, following the relative afferent pupillary defect with neutral density filters?

The visual fields done by Goldmann perimetry not only demonstrate several constriction but also a tendency toward (nonphysiologic) circularization of isopters. This is as limited as 10 degrees surrounding fixation, found in Case 1; this circular isopter raises the question of nonorganic constriction. The involved eye in Case 2 also had a circular (rather than elliptical) isopter and makes the examination suspect. In Case 3 there was expansion of isopters also present in the nonoperated on eye. In Case 4 a circular isopter (horizontally at 40 degrees) was present.

Two issues are critical to interpretation of this type of study. The first concerns the criterion used to determine the presence of progressive visual loss. If only eyes that deteriorated were selected for surgery and the decision was based on less than four fields, regression to the mean could account for some improvement.[2] It is interesting that the improvement in operated on eyes did not exceed the initial visual acuity (before progression occurred).

Secondly, and more importantly, the statement that spontaneous subsequent improvement is rare may be incorrect. Ellenberger, Keltner, and Burde,[3] in their cases of acute optic neuropathy in older patients, found impaired visual acuity improved (at least two lines) in one third of the cases. Hayreh and Podhajsky[4] reported improvement of visual field or Snellen acuity (of at least two lines) in 36.4% of patients with untreated acute anterior ischemic optic neuropathy. Dramatic spontaneous improvement has been reported.[5]

From these data it is premature to conclude, as is stated in the article abstract, that "optic nerve sheath decompression is an effective treatment for patients with nonarteritic ischemic optic neuropathy and progressive visual loss." The issue of the efficacy of optic nerve sheath fenestration for anterior ischemic optic neuropathy is likely to remain unresolved until a controlled study is done. The potential of an effective treatment for the substantial population suffering from the sudden visual loss caused by ischemic optic neuropathy adds to the importance that the data be collected in the most rigorous fashion possible.

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References

1. Ellenberger, C., Jr., Burde, R. M., and Keltner, J. L.: Acute optic neuropathy. Treatment with diphenylhydantoin. Arch. Ophthalmol. 91:435, 1974.
2. Krakau, C. E. T.: A statistical trap in the evaluation of visual field decay. Acta Ophthalmol. 173:19, 1985.
3. Ellenberger, C., Jr., Keltner, J. L., and Burde, R. M.: Acute optic neuropathy in older patients. Arch. Neurol. 28:182, 1973.
4. Hayreh, S. S., and Podhajsky, P.: Visual field defects in anterior ischemic optic neuropathy. Doc. Ophthalmol. Proc. Ser. 19:53, 1982.
5. Kelman, S. E., and Elmon, M. J.: Optic nerve sheath decompression nonarteritic ischemic optic neuropathy improves multiple visual function parameters. Arch. Ophthalmol. 109:667, 1991.

Reply

EDITOR:

We read with interest the concerns expressed by Drs. Wall and Newman. On the basis of our own experience and that of Sergott and associates[1] and Kelman and Elmon,[2] our approach to patients with nonarteritic ischemic optic neuropathy consists of an initial neuro-ophthalmologic examination, including visual fields, optic disk photographs, and standardized echography to measure the diameter of the optic nerve and detect the presence of optic nerve sheath fluid. The patients are then observed closely at weekly intervals for evidence of progressive visual function. Patients with static, that is nonprogressive, visual loss continue to be followed up and are not offered optic nerve sheath decompression unless there is evidence of progression. All patients with evidence for progressive loss of visual acuity and visual field with evidence for accumulated fluid in their optic nerve sheaths are offered optic nerve sheath decompression.

It is our experience[3] and the experience of others[1,2,4] that when performed by experienced surgeons, optic nerve sheath decompression is a relatively benign procedure. In light of three series in the recent literature demonstrating the utility of optic nerve sheath decompression for progressive nonarteritic ischemic optic neuropathy, we cannot, in good conscience, observe patients with progressive visual loss.[1,2]

We appreciate Drs. Wall and Newman's concern about spontaneous improvement in visual function in patients with nonarteritic ischemic optic neuropathy. We have not seen patients with progressive visual loss after an episode of nonarteritic ischemic optic neuropathy demonstrate spontaneous improvement. We have, however, been pleased with the results from intervention by optic nerve sheath decompression in these patients.

In essence, we find, as do others, that optic nerve sheath decompression is a safe, effective treatment for patients with progressive visual loss secondary to nonarteritic ischemic optic neuropathy. It is important to note, as mentioned by Drs. Wall and Newman, that improvement in operated on eyes did not exceed the initial visual acuity and field before progression occurred. Optic nerve sheath decompression cannot resurrect dead axons, infarcted during the initial episode of nonarteritic ischemic optic neuropathy. Subsequently, it is probably not the appropriate treatment for nonprogressive nonarteritic ischemic optic neuropathy. By relieving compression of injured axons in a tight scleral canal, or evacuating a fluid-filled optic nerve sheath, optic nerve sheath decompression retards progressive visual loss and restores visual acuity to the level it was before progression occurred.

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References

1. Sergott, R. C., Cohen, M. S., Bosley, T. M., and Savino, P. J.: Optic nerve decompression may improve the progressive for of nonarteritic ischemic optic neuropathy. Arch. Ophthalmol. 107:1743, 1989.
2. Kelman, S. E., and Elmon, M. J.: Optic nerve sheath decompression for nonarteritic ischemic optic neuropathy improves multiple visual function parameters. Arch. Ophthalmol. 109:667, 1991.
3. Spoor, T. C., Ramocki, J. M., Madion, M., and Wilkinson, M. J.: Treatment of pseudotumor cerebri by primary and secondary optic nerve sheath decompression. Am. J. Ophthalmol. 112:177, 1991.
4. Sergott, R. C., Savino, P. J., and Bosley, T. M.: Modified ONSD provides long-term visual improvement for PTC. Arch. Ophthalmol. 106:1384, 1988.

A Simple Procedure for Complicated Strabismus

EDITOR:

In the article, "A simple procedure for complicated strabismus" by E. G. Buckley and L. M. Townshend (Am. J. Ophthalmol. 111:302, March 1991), a procedure of recession and resection of recti muscles, combined with horizontal or vertical transposition, was described. In 1989 at the Italian Ophthalmological Society Annual Meeting we exhibited a poster concerning a case in which we adopted a similar procedure.[1] The difference is that in our procedure, instead of a recession of the transposed muscle, we performed a lengthening of the tendon with fascia lata. Our patient had a long-term right exotropia and hyperdeviation (primary deviation 50 prism diopters exotropia, 50 prism diopters right hypertropia) with limitation of adduction and infraduction in the right eye. The vertical component was caused by restrictive (forced-duction-test-positive) and paralytic factors (right double depressor palsy). Postoperatively 1½ months after a procedure on the right eye to release restriction (inferior rectus muscle lengthening and bare sclera closure), we performed the transposition procedure, lengthening the lateral rectus muscle (10 mm) and resecting the medial rectus muscle (6 mm), in the same eye. At the same time we performed a recession of the lateral rectus muscle (6 mm) in the contralateral eye. After this procedure, adduction was normal and infraduction was slightly limited. The vertical deviation was well corrected (2 prism diopters of residual right hypertropia) but, despite the amount of horizontal surgical correction, horizontal undercorrection resulted (20 prism diopters exotropia). The procedure had to be performed again on the contralateral eye, lengthening the lateral rectus muscle and resecting the medial rectus muscle, and resulted in good ocular alignment in all positions of gaze. Since then we have operated on two similar patients, performing the same procedure. Results were good; however, after the combined procedure, these patients also showed a horizontal undercorrection.

We agree with the effectiveness of this procedure and its theoretical and practical superiority over traditional ones. Unlike Drs. Buckley and Townshend, we found that, after transposition, on the horizontal deviation results were less than expected. This was likely caused by the transposition, which changes the direction of pull of the muscles, reducing their horizontal effect. Obviously, the presence of a restrictive factor must always to be excluded before performing a transposition procedure. In the presence of a paralytic and restrictive disorder the surgeon must first relieve restriction and then perform the transposition procedure. This required operating on at least three recti muscles in the same eye, and performing multiple procedures may not be sufficient to prevent an anterior segment ischemia.

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Reference

1. Nardi, M., Bartolomei, M. P., and Barca, L.: Knapp transposition procedure with lengthening of lateral rectus muscle and resection of medial rectus muscle. Proceedings of the LXIX Congress of the Italian Ophthalmological Society. Rome, 1989, p. 460.

Reply

EDITOR:

Drs. Nardi and Barca describe an additional case of combined transposition-resect-recession of the horizontal recti muscles. They confirm the effectiveness of this procedure to correct a horizontal and vertical deviation and they raise two concerns about the procedure. Their experience in three patients who had vertical transposition combined with horizontal resect-recession was that the horizontal deviation was undercorrected. They postulated that this was caused by the alteration of the pull of these muscles. Our experience does not confirm this finding. Simply transposing the recti muscles does not limit their action. In a series of full tendon transpositions for sixth-nerve palsy, the ductions of the transposed muscles were entirely normal.[1] In our published series, the amounts of surgery necessary for the resect-recession procedure were typical, and several patients had mild overcorrection. In the case report, the duction limitation was well corrected with the procedure and there is not enough information given to comment on why a residual exodeviation remained postoperatively. One should proceed cautiously in overresecting or recessing muscles when using this technique.

The second issue addressed is the management of a combined restrictive and paralytic motility disorder. We fully agree that a transposition procedure alone should not be performed if the clinical examination demonstrates a significant restrictive component. Even in this situation, however, a combined transposition procedure does allow the surgeon to approach both the horizontal and vertical component, operating on the least number of muscles.

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Reference

1. McManaway, J. W., Buckley, E. G., and Brodsky, M. C.: Vertical rectus muscle transposition with

intraoperative botulinum toxin for the treatment of sixth nerve palsy. Graefe's Arch. Ophthalmol. 228:401, 1990.

Surgical Management of Oculomotor Nerve Palsy

EDITOR:

In the article, "Surgical management of oculomotor nerve palsy" by I. Gottlob, R. A. Catalano, and R. D. Reinecke (Am. J. Ophthalmol. 111:71, January 1991), the authors report that in two of their patients with aberrant regeneration of the oculomotor nerve, a "Kestenbaum-type" procedure on the noninvolved eye resulted in improvement of blepharoptosis. Preoperatively, these patients demonstrated elevation of the blepharoptotic eyelid on lateral gaze. In 1980, we published the use of this technique[1] to achieve the same result. In a prepublication review of our article, a reviewer suggested that this surgical tactic had been previously presented by A. Jampolsky, M.D., at a strabismus meeting.

FRANCIS E. O'DONNELL, JR., M.D.
St. Louis, Missouri

Reply

EDITOR:

We appreciate the comments of Dr. O'Donnell. His article[1] describes one patients with third-nerve palsy and aberrant regeneration to the upper eyelid. A horizontal recess-resect procedure performed on the fixing eye corrected the exotropia and improved the blepharoptosis. In our article we described two similar patients with third-nerve palsy and aberrant regeneration with elevation of the blepharoptotic eyelid on lateral gaze. Recess-resect procedures performed on the noninvolved eyes improved the blepharoptosis.

We regret the oversight in neglecting to cite this article in our list of references.

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Philadelphia, Pennsylvania

Reference

1. O'Donnell, F. E., Del Monte, M., and Guyton, D. L.: Simultaneous correction of blepharoptosis and exotropia in aberrant regeneration of the oculomotor nerve by strabismus surgery. Ophthalmic Surg. 11:695, 1980.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

The Fine Art of Prescribing Glasses, Without Making a Spectacle of Yourself, ed. 2. By Benjamin Milder and Melvin L. Rubin. Gainesville, Florida, Triad Publishing Company, 1991. 526 pages, index, illustrated. $78

Reviewed by H. STANLEY THOMPSON
Iowa City, Iowa

The authors of this book have now been "flipping cross cylinders" for a combined total of more than 80 years, so they have plenty of wisdom to pass along. Somehow they manage to sustain an upbeat, light-hearted style without losing sight of the serious task of teaching refraction skills. This is not an easy thing to do. Dr. Milder's cheerful doggerel heads each chapter and pops up here and there throughout the text. These verses made me feel warm and tolerant (rather than nauseated), which is a measure of the authors' success.

The text is lively and displays intelligence and sympathy for the student refractionist. The first edition has been extraordinarily popular. Most copies are now dog-eared and coffee-stained from long hours of use.

Ophthalmology is fortunate in having an up-to-date second edition of this friendly and accessible book. Every first-year resident should own a copy.

Books Received

Developments in Ophthalmology: Evolution of Microsurgery, vol. 22. Edited by P. Sourdille. Basel, Switzerland, S. Karger AG, 1991. 168 pages, index, illustrated.

This is a record of 33 of the papers given at the La Baule meeting of the International Ophthalmic Microsurgery Study Group in September 1990. The emphasis is on new issues in anterior segment surgery.

Glaucoma Surgical Techniques. Edited by Richard P. Mills and Robert N. Weinreb. San Francisco, American Academy of Ophthalmology, 1991. 180 pages, index, illustrated. $55 for non-members; $40 for members

The Academy is really doing a nice job on these monographs. The materials, the layout, the diagrams, and the use of color are all of the highest quality. And the content isn't bad either! This volume is brought to a gratifying conclusion with a self-study examination.

My Fake Eye, The Story of My Prosthesis. By Nancy Chernus-Mansfield and Marilyn Horn. 23 pages, illustrated. (The books are offered for free; however, donations are welcomed to continue to make other books available.)

This little booklet is directed to parents whose child must have an eye removed. It consists of 17 color photographs with one to three-sentence statements of a child who must have an eye removed and a prosthesis used. It is exceptionally well done and will provide parents with much assistance.

Recovery from Anesthesia. International Anesthesiology Clinics, vol. 29, No. 2. By Philip W. Lebowitz (series editor). Boston, Little, Brown and Company, 1991. 121 pages, index, illustrated. Series subscription $81 per year; single issue, $38

This collection of nine review papers carries the message that emergence from anesthesia is a time for vigilance by anesthesiologists, surgeons, and hospitals. There is still that long, and potentially dangerous, drug hangover to deal with.

Saunders Ophthalmology Word Book. By Joyce Adams. Philadelphia, W. B. Saunders, 1991. 362 pages. $23.95

This is a list of 12,000 words and phrases of ophthalmology. No definitions are offered, but, with the imprint of a well-known publishing house, one can at least assume the words are correctly spelled. It will be popular with typists who work for ophthalmologists.

The Book List

Color Atlas of Ophthalmic Surgery: Corneal and Refractive Surgery. By Herbert E. Kaufman, Bruce A. Barron, Marguerite B. McDonald, and Steven E. Wilson. Philadelphia, J. B. Lippincott Company, 1991. 337 pages, index, illustrated. $150

International Ophthalmology Clinics: Systemic Associations of Ocular Disorders. Edited by Daniel H. Gold. Boston, Little, Brown and Company, 1991. 184 pages, index, illustrated. Subscription price per year, $81; single, nonsubscriber, $38

L'Annee Therapeutique et Clinique en Ophtalmologie, Volume XLI. By A. Dubois-Poulsen. Paris, Diffusion Generale de Librairie, 1990. 283 pages, index, illustrated. (no price given)

Medikamentose Augentherapie, third edition. By Paul U. Fechner and Klaus D. Teichmann. Germany, Ferdinand Enk Verlag Stuttgart, 1991. 366 pages, index, illustrated. (no price given)

Pictorial Communication in Virtual and Real Environments. Edited by Stephen R. Ellis. Bristol, PA, Taylor & Francis, 1991. 603 pages, index, illustrated. $91

Veterinary Ophthalmology, second edition. Edited by Kirk N. Gelatt. York, PA, Williams & Wilkins, 1991. 765 pages, index, illustrated. $125

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Removal of lens epithelial cells by dispersion with enzymatic treatment followed by aspiration. Nishi, O.*, Nishi, K., and Hikida, M.: Ophthalmic Surg. 22:444, 1991.

LENS EPITHELIUM, OPACIFIED POSTERIOR CAPSULE, DISPERSION WITH NEUTRAL PROTEASE

Lenses were removed by phacoemulsification in a group of rabbits. A neutral protease (Dispase) was diluted in sodium hyaluronate and doses between 300 and 1,000 pu/ml were injected into the lens capsule. After two minutes, the epithelial cells and the sodium hyaluronate were removed by irrigation and aspiration. All doses of the neutral protease were effective in loosening the attachment of the epithelial cells to the capsule so that the cells could be readily observed and aspirated. The enzyme had no effect on corneal thickness or corneal endothelial cell density. Light microscopy of the cornea, zonules, and other tissues showed no evidence of damage. These experiments suggested that neutral protease may be helpful in the safe removal of lens epithelial cells.—Michael A. Kass

*Nishi Eye Hospital, 4-14-26 Nakamichi, Higashinari-ku, Osaka 537, Japan.

Use of high-density vitreous substitutes in the removal of posteriorly dislocated lenses or intraocular lenses. Liu, K.-R., Peyman, G. A.*, Chen, M.-S., and Chang, K.-B.: Ophthalmic Surg. 22:503, 1991.

DISLOCATED LENS, DISLOCATED INTRAOCULAR LENS, HIGH-DENSITY VITREOUS SUBSTITUTES

High-density vitreous substitutes were used to remove four dislocated crystalline lenses and three dislocated intraocular lenses from vitreous cavities. Fluorosilicone oil was used to remove the four crystalline lenses and one of the intraocular lenses. Perfluorophenanthrene was used to remove the other two dislocated intraocular lenses. The high-density vitreous substitutes were injected into the vitreous cavity through the pars plana, causing the crystalline lenses or intraocular lenses to float forward so that they could be removed through limbal incisions. The vitreous substitutes were then removed from the vitreous cavity. No intraoperative or postoperative complications of this approach were observed.—Michael A. Kass

*LSU Eye Center, 2020 Gravier St., Ste. B, New Orleans, LA 70112-2234.

Ophthalmic complications of spina bifida and hydrocephalus. Gaston, H.: Eye 5:279, 1991.

SPINA BIFIDA, HYDROCEPHALUS, STRABISMUS, NYSTAGMUS, PAPILLEDEMA, OPTIC ATROPHY

A group of 322 children who had spina bifida, hydrocephalus, or both conditions, were examined. Ocular abnormalities were common in this group, and only 86 of the 322 children (27%) had visual acuity of 20/20 in both eyes with full visual fields and good stereopsis. One hundred thirty-six children (42%) had strabismus, 93 (29%) had lateral rectus muscle palsy or nystagmus, 44 (14%) had papilledema, and 55 (17%) had optic atrophy. Over a six-year follow-up period, 53 episodes of increased intracranial pressure were observed. Ocular abnormalities including papilledema, sun-setting syndrome, blurred vision, Parinaud's syndrome, convergent squint, and lateral rectus muscle palsy were detected in 37 of these 53 episodes (70%). In many cases, ophthalmic examination provided initial clues of increased intracranial pressure.—Michael A. Kass

Southampton Eye Hospital, Wilton Ave., Southampton S09 4XW, Great Britain.

Ocular manifestations in fetal alcohol syndrome. Chan, T.*, Bowell, R., O'Keefe, M., and Lanigan, B.: Br. J. Ophthalmol. 75:524, 1991.

FETAL ALCOHOL SYNDROME, OCULAR INVOLVEMENT, EYELID ABNORMALITIES, OPTIC NERVE HYPOPLASIA

The fetal alcohol syndrome is characterized by marked pre- and postnatal growth deficiency, central nervous system involvement, and a typical facies with microcephaly, microphthalmia, short palpebral fissures, long philtrum, thin upper lip, and flattening of the maxillary area. Eight children with fetal alcohol syndrome underwent ocular examination. The mothers of the children had histories of alcohol abuse throughout pregnancy, especially in the first trimester. All of the children had ocular abnormalities, including short palpebral fissures, Peters' anomaly, lens opacification, strabismus, and nystagmus. Four of the eight children (50%) had optic nerve hypoplasia. These findings suggest that all children with fetal alcohol syndrome should undergo careful ocular examination.—Michael A. Kass

*Hinchingbrooke Hospital, Hinchingbrooke Park, Huntingdon, Cambs PE18 8NT, Great Britain.

Deficiencies in human neonates' color vision: photoreceptoral and neural explanations. Adams, R. J.*, Courage, M. L., and Mercer, M. E.: Behav. Brain Res. 43:109, 1991.

VISUAL DEVELOPMENT, COLOR VISION, INFANTS

A group of 40 neonates (mean age, 3.2 days) underwent testing of color vision. Color vision was tested with chromatic-achromatic discriminations in the midspectral region by using a habitation procedure with measures to minimize achromatic cues. The newborns could discriminate orange (wave length, 595 nm) but not yellow-green (wave length, 565 nm) lights from achromatic lights of varying luminance. These and previous results implied that newborns have at least dichromatic color vision. However, newborns have relatively poor chromatic-achromatic discrimination in the short wave lengths (470 to 480 nm) and in the medium wave lengths (565 nm). Several possible explanations for this phenomenon include an immaturity of the preneural (photoreceptoral and optical) mechanisms, immaturity of the short wavelength-sensitive cones, or immaturity of the blue/yellow opponent channel.—Michael A. Kass

*Department of Psychology, Memorial University of Newfoundland, St. John's, Newfoundland, Canada.

Effect of very low birth weight and subnormal head size on cognitive abilities at school age. Hack, M.*, Breslau, N., Weissman, B., Aram, D., Klein, N., and Borawski, E.: N. Engl. J. Med. 325:231, 1991.

LOW BIRTH WEIGHT, PERINATAL GROWTH FAILURE, POOR ACADEMIC ACHIEVEMENT

Perinatal growth failure is common among infants with birth weights less than 1.5 kg. A group of 249 low birth-weight children monitored since their births between 1977 and 1979 were examined at 8 to 9 years of age. The children underwent neurologic examinations, as well as various intelligence and aptitude tests. Of the 249 children, 33 (13.3%) had perinatal growth failure, such that their head size was more than 2 standard deviations from the mean by 8 months of age. The children with subnormal head size at 8 months of age had a higher incidence of neurologic impairment and lower mean intelligence scores. In multiple regression analyses to control for socioeconomic and neonatal risk factors, a subnormal head size at 8 months of age had an independently adverse effect on intelligence as well as on scores for receptive language, speech, reading, and spelling. In low birth-weight infants, perinatal growth failure, as defined by a subnormal head circumference at 8 months of age, was associated with poor cognitive function, low academic achievement, and a higher incidence of hyperactivity at 8 years of age.—Michael A. Kass

*Rainbow Babies and Children's Hospital, University Hospitals of Cleveland, 2101 Adelbert Rd., Cleveland, OH 44106.

The effect of transcutaneous electrical nerve stimulation on ocular pain. Whitacre M. M.: Ophthalmic Surg. 22:462, 1991.

OCULAR PAIN, TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

The effect of transcutaneous electrical nerve stimulation on pain originating in the eye was studied in ten patients. In each patient one electrode was applied to the temple and another was applied to the middle of the brow on the affected side. The transcutaneous electrical nerve stimulator was turned on and the output power was increased until the patient felt a slight tingling or twitching sensation. The treatment was continued for approximately 30 minutes. Three patients who received transcutaneous electrical nerve stimulation during panretinal photocoagulation reported marked reduction of pain. Three of five patients who had persistent pain after scleral buckling procedures with or without vitrectomy reported partial or complete relief of pain during the application of transcutaneous electrical nerve stimulation. Three additional patients who had pain after retinal cryopexy, paracentesis, or cyclocryotherapy had no relief of pain with this technique. The study suggested that transcutaneous electrical nerve stimulation may be useful as a substitute for retrobulbar block in laser photocoagulation or as an adjunct to oral analgesics in the management of chronic ocular pain in some patients.—Michael A. Kass

Department of Ophthalmology, Sudler Hall, University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS 66103.

Preherpetic neuralgia. Gilden, D. H.*, Dueland, A. N., Cohrs, R., Martin, J. R., Kleinschmidt-DeMasters, B. K., and Mahalingam, R.: Neurology 41:1215, 1991.

HERPES ZOSTER, NEURALGIA

Herpes zoster is characterized by a vesicular rash and pain localized to a specific dermatome. Generally, the rash and pain develop together, or the pain precedes the rash by several days. Six patients with herpes zoster in whom the pain preceded the rash by seven to more than 100 days were examined. The pain was severe, burning, and radicular, and was located in dermatomes different from, as well as the same as, those of eventual rash. One patient developed disseminated herpes zoster with paresis. Another patient developed fatal herpes zoster encephalitis. Both patients had undergone long-term treatment with low-dose corticosteroids. A third patient with preherpetic neuralgia had a history of metastatic carcinoma. A fourth individual had a history of brachial neuritis. The other two patients with preherpetic neuralgia had no apparent underlying disease. It thus appears that, in certain cases, pain can precede the rash of herpes zoster by weeks to months.—Michael A. Kass

*Department of Neurology, 4200 E. 9th Ave., Campus Box B-182, Denver, CO 80262.

Treatment of migraine attacks with sumatriptan. The Subcutaneous Sumatriptan International Study Group: N. Engl. J. Med. 325:316, 1991.

MIGRAINE HEADACHES, SUMATRIPTAN

A group of 639 patients with migraines were randomly assigned to receive placebo or subcutaneous injections of 6 or 8 mg of sumatriptan, a selective agonist of receptors resembling 5-hydroxytryptamine. After 60 minutes, the severity of headache was decreased in 72% of the 422 patients given 6 mg of sumatriptan, in 79% of the 109 patients given 8 mg of sumatriptan, and in 25% of the 105 patients given placebo. After 120 minutes, 86% to 92% of the 511 patients treated with sumatriptan had improvement in the severity of headache, as compared with only 37% of the 104 patients who received placebo. Twenty-one patients were excluded from the analysis because of missing data or protocol violations. Adverse events were minor and transient in all groups. A single 6-mg dose of sumatriptan given subcutaneously appeared to be a highly effective, rapidly acting, and well-tolerated treatment for migraines. Administration of a second dose 60 minutes later to patients who did not respond well to an initial dose seemed to offer little additional benefit.—Michael A. Kass

*Dr. Michel D. Ferrari, Department of Neurology, University Hospital, P.O. Box 9600, 2300 R C Leiden, The Netherlands.

Treatment of acute cluster headache with sumatriptan. The Sumatriptan Cluster Headache Study Group: N. Engl. J. Med. 325:322, 1991.

SUMATRIPTAN, CLUSTER HEADACHE

A double-masked, placebo-controlled crossover study in which patients were randomly assigned to treatment was performed to assess the efficacy and tolerability of sumatriptan in 49 patients with cluster headache. The patients randomly received a subcutaneous injection of 6 mg of sumatriptan for one cluster headache attack or placebo for another attack. The results for the two attacks could be fully evaluated in 39 patients. Response to treatment was defined as complete or almost complete relief of headache within 15 minutes of the injection. The severity of the headache decreased in 74% of the attacks within 15 minutes of treatment with sumatriptan as compared to 26% of the attacks for which placebo was administered ($P < .001$). Thirty-six percent of the patients were free of pain within ten minutes after the administration of sumatriptan as compared to 3% after administration of placebo; by 15 minutes, 46% and 10% of patients, respectively, were free of pain. The functional disability and the incidence of ipsilateral conjunctival injection also decreased more in response to sumatriptan than placebo. No serious adverse events occurred. Sumatriptan appears to be an effective and well-tolerated treatment for acute attacks of cluster headaches.—Michael A. Kass

*Dr. Karl Ekbom, Department of Neurology, Söder Hospital, S-11883 Stockholm, Sweden.

High frequency of asymptomatic visual field defects in subjects with transient ischaemic attacks or minor strokes. Falke, P.*, Abella, B. M., Jr., Krakau, C. E. T., Lilja, B., Lindgärde F., Maly, P., and Stavenow, L.: J. Intern. Med. 229:521, 1991.

VISUAL FIELD DEFECTS, TRANSIENT ISCHEMIC ATTACKS, MINOR STROKES

By definition patients with transient ischemic attacks have no focal, neurologic dysfunction that lasts more than 24 hours. Many of these patients, however, have cerebral infarctions that are visible on computerized tomography or pathologic findings disclosed by cerebral blood-flow studies. Twenty-two consecutive men with transient ischemic attacks and 18 men with minor strokes underwent perimetric examination. Asymptomatic visual field defects were found in five of 17 patients (29%) who had a history of transient ischemic attacks and eight of 14 patients (57%) who had a history of minor stroke. Eleven of the 13 scotomas (85%) were solely or predominantly located in the upper part of the visual field. These patients underwent computed tomography and studies of regional cerebral blood flow. Unsuspected cerebral infarctions were found in the symptomatic hemisphere in seven of 20 (35%) patients with transient ischemic attacks, and 11 of 18 (61%) patients with minor strokes. Abnormal cerebral blood flow in the symptomatic hemisphere was found in 17 of 20 (85%) patients with transient ischemic attacks and in 13 of 17 (76%) patients with minor strokes. The authors propose that the visual field defects seen in these patients were the result of multiple small cerebral infarctions caused by microemboli.—Michael A. Kass

*Department of Internal Medicine, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden.

Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators: N. Engl. J. Med. 325:445, 1991.

CAROTID VASCULAR DISEASE, CAROTID ENDARTERECTOMY

The role of carotid endarterectomy in the treatment of patients with carotid vascular disease has been long debated. A trial in which patients were randomly assigned to treatment was conducted at 50 medical centers throughout the United States and Canada. The study consisted of 659 patients who had 70% to 99% carotid stenosis, and who had had a previous hemispheric or retinal transient ischemic attack or a nondisabling stroke within 120 days. All patients received medical care, including antiplatelet therapy, and those assigned to surgical treatment underwent carotid endarterectomy. Patients were examined by masked observers at one, three, six, nine, and 12 months after entry and every four months thereafter. Life-table estimates of the cumulative risk of ipsilateral stroke at two years were 26% in the 331 medical patients and 9% in the 328 surgical patients ($P < .001$). For a major or fatal ipsilateral stroke, the corresponding estimates were 13.1% and 2.5%, respectively ($P < .001$). Thus, it appears that carotid endarterectomy is beneficial to patients with recent hemispheric or retinal transient ischemic attacks or nondisabling strokes and ipsilateral high-grade carotid artery stenosis.—Michael A. Kass

D. W. Taylor, Department of Clinical Epidemiology and Biostatistics, McMaster University, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada.

A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. Stampfer, M. J.*, Sacks, F. M., Salvini, S., Willett, W. C., and Hennekens, C. H.: N. Engl. J. Med. 325:373, 1991.

MYOCARDIAL INFARCTION, CHOLESTEROL, LIPOPROTEIN

Blood samples were collected at baseline from 14,916 men who participated in the Physicians' Health Study. The physicians ranged from 40 to 84 years of age at baseline. After five years of follow-up, plasma samples from 246 men with new myocardial infarctions were analyzed together with specimens from 246 men matched for age and smoking status who had not had myocardial infarctions. The subjects who had myocardial infarctions had higher prevalences of hypertension, angina, and diabetes mellitus. This group also had higher levels of total cholesterol, higher ratios of total to high-density lipoprotein cholesterol, markedly lower levels of high-density lipoprotein cholesterol, and lower levels of the HDL_2 and HDL_3 subfractions. This study underscored the importance of high-density lipoprotein cholesterol in predicting the risk of myocardial infarction and demonstrated protective effects of both the HDL_2 and HDL_3 subfractions of high-density lipoprotein cholesterol. Little or no predictive value for the levels of apolipoproteins A-I or A-II was observed. Multivariate analysis suggested that the ratio of total to high-density lipoprotein cholesterol was the best predictor of myocardial infarction.—Michael A. Kass

*Channing Laboratory, 180 Longwood Ave., Boston, MA 02115.

Differences in the use of procedures between women and men hospitalized for coronary heart disease. Ayanian, J. Z., and Epstein, A. M.*: N. Engl. J. Med. 325:221, 1991.

CORONARY ANGIOGRAPHY, CORONARY REVASCULARIZATION, RATES IN MEN AND WOMEN

Previous studies have reported differences in major diagnostic and therapeutic procedures for men and women with coronary heart disease. To assess whether these differences can be generalized, a retrospective analysis of coronary angiography and revascularization was performed in men and women hospitalized for coronary heart disease in 1987. Data were reviewed on 49,623 patients discharged in Massachusetts and 33,159 patients discharged in Maryland. A multiple logistic regression was performed to estimate the adjusted odds of the use of a procedure controlling for principal diagnosis, age, secondary diagnosis of congestive heart failure or diabetes mellitus, race, and insurance status. The adjusted odds of undergoing angiography were 28% and 15% higher for men than for women in Massachusetts and Maryland, respectively. The respective adjusted odds of undergoing revascularization were 45% and 27% higher for men than for women. Because these differences could be related to differing thresholds for hospital admission, a second analysis was performed and limited to patients with diagnosed acute myocardial infarction, a group in which all patients would be expected to receive hospital care. The male-to-female odds ratios in both states remained similar in magnitude and were statistically significant for angiography and revascularization. These differences suggested that women who are hospitalized for coronary heart disease undergo fewer major diagnostic and therapeutic procedures than men. They may represent appropriate levels of care for men and women, but it is also possible that they reflect underuse in women or overuse in men.—Michael A. Kass

*Department of Health Care Policy, Harvard Medical School, 25 Shattuck St., Parcel B, 1st Floor, Boston, MA 02115.

Sex differences in the management of coronary artery disease. Steingart R. M.*, Packer, M., Hamm, P., Coglianese, M. E., Gersh, B., Geltman, E. M., Sollano, J., Katz, S., Moyé, L., Basta, L. L., Lewis, S. J., Gottlieb, S. S., Bernstein, V., McEwan, P., Jacobson, K., Brown, E. J., Kukin, M. L., Kantrowitz, N. E., Pfeffer, M. A., For the Survival and Ventricular Enlargement Investigators: N. Engl. J. Med. 325:226, 1991.

CORONARY HEART DISEASE, CARDIAC CATHETERIZATION, CORONARY BYPASS SURGERY, THERAPY IN MEN AND WOMEN

Coronary artery disease is the leading cause of death among women. However, previous studies have suggested that women with coronary artery disease often receive less aggressive treatment than men do. In the present study men and women who were enrolled in a large postmyocardial infarction intervention trial were interviewed about previous care. The nature and severity of anginal symptoms and the use of antianginal and anti-ischemic interventions before enrollment in the trial were assessed in 1,842 men and 389 women who survived acute myocardial infarction. Before the infarction, women were as likely as men to have had angina and to have been treated with antianginal drugs. However, fewer women had undergone cardiac catheterization (15.4% of women, compared to 27.3% of men, $P < .001$) or coronary bypass surgery (5.9% of women, compared to 12.7% of men, $P < .001$). When these differences were adjusted for important covariates, men were still twice as likely to undergo an invasive cardiac procedure than women were. However, bypass surgery was performed with equal frequency among the men and women who underwent cardiac catheterization. This study suggested that physicians pursue a less aggressive management approach to coronary disease in women than in men.—Michael A. Kass

*Winthrop-University Hospital, 259 First St., Mineola, NY 11501.

Psychological stress and susceptibility to the common cold. Cohen, S.*, Tyrrell, D. A. J., and Smith, A. P.: N. Engl. J. Med. 325:606, 1991.

RESPIRATORY INFECTION, PSYCHOLOGICAL STRESS

After completing questionnaires assessing their degree of psychologic stress, 394 healthy subjects were given nasal drops containing one of five respiratory tract viruses. An additional 26 patients were given saline nasal drops. The subjects were then quarantined and monitored for the development of upper respiratory tract infection as determined by clinical symptoms and by the isolation of virus or an increase in virus-specific antibody titers. The rates of increase of both respiratory tract infection and clinical colds corresponded in a dose-response manner to increases in the degree of psychologic stress. Infection rates ranged from approximately 74% to approximately 90% according to degree of psychologic stress, and the incidence of clinical colds ranged from approximately 27% to 47%. These results were not altered when the authors controlled for the effects of age, gender, education, allergic status, weight, season, smoking, alcohol consumption, exercise, diet, quality of sleep, white blood cell counts and total immunoglobulin levels. Thus, psychologic stress was associated in a dose-response manner with an increased risk of acute infectious respiratory tract illness. This risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection.—Michael A. Kass

*Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213.

Erythropoietin and visual hallucinations. Steinberg, H.: N. Engl. J. Med. 325:285, 1991.

ERYTHROPOIETIN, VISUAL HALLUCINATIONS

Recombinant human erythropoietin is widely used to treat the anemia of chronic renal failure in patients treated with dialysis. Five patients being treated with hemodialysis who were receiving erythropoietin developed visual hallucinations. None of these patients had any evidence of delirium or psychosis, and no other medication or physical condition that could account for the visual hallucinations was observed. The hallucinations consisted of objects moving in front of the patients, such as people, cartoon figures, animals, or birds. The patients were often puzzled and curious but not terrified by the hallucinations. The hallucinations occurred after the patients had received erythropoietin for two to 13 months in dosages ranging from 2,000 units once a week to 4,000 units three times a week. Four patients stopped taking erythropoietin and the visual hallucinations disappeared within one to three weeks. All four patients later resumed erythropoietin treatment and two had recurrences within three to four weeks, which disappeared again after the erythropoietin treatment was stopped. The fifth patient was treated with perphenazine, but continued to take erythropoietin; the hallucinations disappeared and did not recur after treatment with perphenazine was stopped.—Michael A. Kass

Long Island Jewish Medical Center, New Hyde Park, NY 11042.

Metipranolol-associated granulomatous anterior uveitis. Akingbehin, T.*, and Villada, J. R.: Br. J. Ophthalmol. 75:519, 1991.

METIPRANOLOL, GRANULOMATOUS ANTERIOR UVEITIS

The charts of 247 glaucoma patients who were treated with metipranolol were reviewed. Fifteen patients (26 eyes) had one or more episodes of granulomatous anterior uveitis. These episodes were characterized by large, keratic precipitates, flare, and cells. In more than half of the episodes, the acute inflammation was associated with an increase in intraocular pressure. Metipranolol 0.6% was implicated in 54 of the 56 episodes of uveitis. Metipranolol 0.3% was implicated in the remaining two. Fifty-one other cases of presumed metipranolol-associated granulomatous anterior uveitis have been reported to the British committee on safety of medicines. As a result, multidose metipranolol in 0.1%, 0.3%, and 0.6% strengths has been withdrawn from clinical use in the United Kingdom. The pathogenesis of this adverse drug reaction is uncertain.—Michael A. Kass

*Department of Ophthalmology, District General Hospital, Southport PR8 6 NJ, Great Britain.

Factors associated with poor visual outcome in acute retinal necrosis. Matsuo, T.*, Morimoto, K., and Matsuo, N.: Br. J. Ophthalmol. 75:450, 1991.

RETINAL NECROSIS, VISUAL OUTCOME

We reviewed 22 consecutive patients (26 eyes) with acute retinal necrosis to elucidate whether there was any sign at an early stage to predict poor visual outcome. Final visual acuity of the patients fell into two groups, one worse than 20/600 (15 eyes) and the other better than 20/30 (11 eyes). The patients with poor visual outcome showed diffuse retinal arteritis or arterial obliteration which was associated with reduced amplitude of electroretinographic a and b waves and elevated levels of circulating immune complex, even at an early stage when retinal exudates were still localised to the peripheral fundus. The retinal exudates in these patients extended rapidly to the posterior pole. In contrast, the patients with good visual outcome showed retinal arteritis limited rapidly to the posterior pole. In contrast, the patients with good visual outcome showed retinal arteritis limited within retinal exudates throughout the course. These signs at an early stage can be used as prognostic factors to manage patients with acute retinal necrosis more constructively.—Authors' abstract

*Department of Ophthalmology, University of British Columbia, 2550 Willow St., Vancouver, BC, V5Z 3N9 Canada.

Ocular cicatricial pemphigoid occurring as a sequela of Stevens-Johnson syndrome. Chan, L. S.*, Soong, H. K., Foster, C. S., Hammerberg, C., and Cooper, K. D.: JAMA 266:1543, 1991.

CICATRICIAL PEMPHIGOID, STEVENS-JOHNSON SYNDROME

Five patients developed ocular cicatricial pemphigoid after an acute episode of severe ocular inflammatory disease caused by Stevens-Johnson syndrome. The interval between the onset of Stevens-Johnson syndrome and the development of cicatricial pemphigoid ranged from a few months to 31 years. In all five patients, linear immune deposits characteristic of cicatricial pemphigoid were present along the basement membrane zone in mucosal biopsy specimens. They were detected by either direct immunofluorescence microscopy or direct immunoperoxidase staining. Severe ocular mucosa injury such as that which occurs in Stevens-Johnson syndrome may be a precipitating factor for the development of ocular cicatricial pemphigoid.—Michael A. Kass

*Department of Dermatology, Immunodermatology Unit, University of Michigan Medical Center, R5538 Kresge 1, Box 0530, Ann Arbor, Ml 48109-0530.

Correction

In the Letter to THE JOURNAL, "Mixing fortified antibiotic eyedrops," by R. J. Schechter (Am. J. Ophthalmol. 112:450, October 1991), the fourth paragraph was incorrect as printed. The paragraph should read as follows:

The calculations are straightforward. Gentamicin is available as a commercial eyedrop as 5 ml in a concentration of 3 mg/ml. Thus the mixture contains 15 mg. Intravenous gentamicin is available in a concentration of 40 mg/ml. Thus adding 1 ml of the intravenous mixture to the bottle results in 55 mg in 6 ml, or about 9.2 mg/ml. Adding 1.5 ml results in 75 mg in 6.5 ml or 11.5 mg/ml. Adding 2 ml results in 95 mg in 7 ml or 13.6 mg/ml. Adding 2.5 ml results in 115 mg in 7.5 ml or 15.3 mg/ml.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

All India Ophthalmological Society: Golden Jubilee Conference

The All India Ophthalmological Society will hold its Golden Jubilee Conference in New Delhi, India, Feb. 2–6, 1992. For more information, contact Dr. Hari Mohan, AIOS, 11-B, Gangaram Hospital Marg, New Delhi-110 060, India; telephone 5733882, 587655; fax 91-11-5728969.

Cullen Eye Institute: Clinical Advances in Ophthalmology

The Cullen Eye Institute of the Baylor College of Medicine will offer a course, Clinical Advances in Ophthalmology for the Practicing Ophthalmologist, March 13–15, 1992, at the Houstonian Hotel in Houston, Texas. For more information, write Carol Soroka, Office of Continuing Education, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030; telephone (713) 798-6020.

New York Eye & Ear Infirmary: Retina Fluorescein and Laser Photocoagulation Course

The New York Eye & Ear Infirmary will sponsor the Retina Fluorescein and Laser Photocoagulation Course March 6 and 7, 1992. For more information, write Sylvia Sorrentino, Institute for Continuing Medical Education, New York Eye & Ear Infirmary, 2nd Ave. at 14th St., New York, NY 10003; telephone (212) 979-4444 or (212) 979-4430.

Edward S. Harkness Eye Institute: Residents' Basic Science Course in Ophthalmology

The Edward S. Harkness Eye Institute of Columbia University will offer its annual Basic Science Course Jan. 6–31, 1992. For additional information, write Clara Duffy, Edward S. Harkness Eye Institute, Box 20, 635 W. 165th St., New York, NY 10032; telephone (212) 305-2725.

Edward S. Harkness Eye Institute: Hands-on Cadaver Dissection

The Edward S. Harkness Eye Institute will sponsor a Hands-on Cadaver Dissection of the Eyelids, Lacrimal System, and Orbit, at the College of Physicians and Surgeons and Columbia-Presbyterian Medical Center in New York Jan. 27 and 28, 1992. For further information, write John C. Merriam, M.D., E. S. Harkness Eye Institute, 635 W. 165th St., New York, NY 10032; telephone (212) 305-5402.

Manhattan Eye, Ear & Throat Hospital: Excimer Laser Seminar

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold an Excimer Laser Seminar Feb. 1, 1992, in New York City. For additional information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

New York Society for Clinical Ophthalmology: Spring Meeting

The New York Society for Clinical Ophthalmology Spring Meeting will be held March 28, 1992, at the New York Waldorf Astoria Hotel. For additional information, write Francine Leinhardt, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200 ext. 2776; fax (212) 832-9126.

Tennessee Academy of Ophthalmology: Annual Meeting

The Tennessee Academy of Ophthalmology will hold its Annual Meeting April 10, 1992, at the Opryland Hotel in Nashville, Tennessee. For more information, write Sue Carson-

Chasteen, TAO, 133 Lucinda Court, Franklin, TN 37064-2943; telephone (615) 794-1851.

Wilmer Ophthalmological Institute: Recent Advances in the Management of Age-Related Macular Degeneration

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor Recent Advances in the Management of Age-Related Macular Degeneration: Guidelines from Recent Clinical Trials Jan. 25, 1992, at the Thomas B. Turner Building, Johns Hopkins Medical Institutions in Baltimore, Maryland. For further information, write Program Coordinator, Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 20, Baltimore, MD 21205-2195; telephone (301) 955-2959.

Personal

Norman Ashton

Professor Norman Ashton of London received the 1991 Pisart Vision Award of The Lighthouse, Inc., for his contributions to visual science. This award annually honors an individual for outstanding contribution to the prevention, cure, or treatment of blindness or vision impairment. Professor Ashton established and was director of the Department of Pathology of the Institute of Ophthalmology at the University of London. After retiring from the chair of pathology, he helped found Fight For Sight, Inc., in London and is currently chairman.

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AMERICAN JOURNAL
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The Role of Ciprofloxacin in the Antibacterial Therapy of Bacterial Keratitis and Bacterial Conjunctivitis

Supplement to THE AMERICAN JOURNAL OF OPHTHALMOLOGY

Preface
Howard M. Leibowitz

A Review of Bacterial Keratitis and Bacterial Conjunctivitis
Michael B. Limberg

Current Therapy for Bacterial Keratitis and Bacterial Conjunctivitis
Roger F. Steinert

Microbiologic Aspects of Fluoroquinolones
Harold C. Neu

Insights From Experimental Data on Ciprofloxacin in the Treatment of Bacterial Keratitis and Ocular Infections
Clifton D. Cokingtin and Robert A. Hyndiuk

Antibacterial Effectiveness of Ciprofloxacin 0.3% Ophthalmic Solution in the Treatment of Bacterial Conjunctivitis
Howard M. Leibowitz

Clinical Evaluation of Ciprofloxacin 0.3% Ophthalmic Solution for Treatment of Bacterial Keratitis
Howard M. Leibowitz

Conclusion
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Preface

Bacterial infection of the cornea is a threat to vision. Even less severe forms require urgent treatment, whereas the more severe forms constitute ocular emergencies. Bacterial infection of the conjunctiva generally is far less serious than its corneal counterpart, but it is far more prevalent. Bacterial conjunctivitis can be incapacitating and the source of more disastrous ocular infections. Therefore, treatment is indicated.

All bacterial infections are treated with antibiotics. Fortunately, most antibiotics are intrinsically active: they do not first have to undergo metabolic changes in some organ distant from the eye in order to exert an antibacterial effect. Consequently, high corneal antibiotic concentrations can be obtained, and efficacy in the tissues of the ocular surface can be assured, simply by administering the medication directly to the infected cornea or conjunctiva.

It is impossible to identify the specific causal organism or its antibiotic sensitivity by clinical examination with the slit-lamp biomicroscope. A Gram stain of material from a corneal scraping or a conjunctival swab may be of value, but the data it provides are not sufficiently reliable to form the basis for the initial choice of antibiotics. Both gram-positive and gram-negative bacteria can cause bacterial keratitis and conjunctivitis, and initial antibiotic therapy must be designed to cover virtually all bacteria. To date, no single antibiotic has a sufficiently wide spectrum of action to fulfill this requirement. Most authorities recommend the use of at least two antibiotics until the causal organism and its antibiotic susceptibility are documented.

It is widely believed that commercially available preparations of ophthalmic antibiotics contain an insufficient concentration of drug to produce maximal inhibition of bacterial growth in the cornea after topical administration. Commonly, the ophthalmologist or the local pharmacist formulates higher concentrations of these antibiotics by using standard parenteral products and an artificial tear preparation as the ophthalmic vehicle. Instructions for preparing these concentrated or fortified antibiotic formulations appear in all standard texts on corneal and external disease. Their use is based on the observation that up to a point, the amount of drug penetrating into and through the cornea increases as the concentration of the formulation increases, and presumably this results in greater antibacterial effect. The concentrated preparations tend to be more irritating than commercial formulations, but they generally do not cause serious toxicity. They are almost universally administered as initial treatment for all but the most minor corneal ulcers, and they have proven to be highly effective.

The earliest quinolone analogue, nalidixic acid, was discovered in 1962 and used clinically in 1963. It had a narrow spectrum of action, and bacterial resistance developed rapidly such that its use was confined to uncomplicated urinary tract infections. Subsequently, the 6-fluoro-7-piperazine-4-quinolones were developed, creating a novel class of broad spectrum antibiotics that differ from nalidixic acid in increased potency, increased spectrum of antibacterial activity, and decreased frequency of spontaneous bacterial resistance. Overall, perhaps their most important property is rapid absorption after oral administration; this produces serum levels sufficient to render many systemic infections susceptible to oral therapy. Fluoroquinolones are active against a broad spectrum of both gram-positive and gram-negative bacteria. Among these compounds, ciprofloxacin currently appears to be the most attractive in terms of oral administration, antibacterial spectrum/activity, pharmacokinetics (twice-daily dosage), lack of adverse side effects, and rare emergence of significant resistance.

Ciprofloxacin is commercially available for topical ophthalmic administration. In this monograph, "The Role of Ciprofloxacin in the Antibacterial Therapy of Bacterial Keratitis and Bacterial Conjunctivitis," Michael B. Limberg, M.D., initially reviews clinical aspects of the two disorders, and Roger F. Steinert, M.D., reviews current principles of treatment. Harold C. Neu, M.D., describes the fluoroquinolones and their role in system disease. Clifton D. Cokingtin, M.D., and Robert A. Hyndiuk, M.D., examine the experimental data that led to the development of this drug as an ophthalmic agent. Finally, Howard M. Leibowitz, M.D., presents the results of topical therapy with commercially available ciprofloxacin 0.3% ophthalmic solution when used as the only agent to treat clinical bacterial keratitis, and the antibacterial effectiveness of ciprofloxacin 0.3% in clinical bacterial conjunctivitis.

HOWARD M. LEIBOWITZ, M.D.

A Review of Bacterial Keratitis and Bacterial Conjunctivitis

Michael B. Limberg, M.D.

Bacterial keratitis is an opportunistic infection of the avascular corneal stroma, initiated by a breakdown of the epithelial barrier. Corneal abrasion with infected material, extended-wear contact lenses, eyelid disease, and disorders of the ocular surface are predominant contributing factors. Acute bacterial conjunctivitis occurs when sufficient bacteria are introduced into the fornices to overwhelm normal bacteriostatic and flushing mechanisms. Chronic conjunctivitis is associated with a constant adnexal source of bacteria and resolves when the source is successfully treated. Rapid diagnosis and treatment of bacterial keratitis are essential to limit stromal scarring and minimize visual loss.

THE CONJUNCTIVA and its adnexa are usually sterile at birth and are rapidly colonized by saprophytic bacteria. Once established, the normal flora develops a lifelong relationship with the host in a stable balance between bacteria proliferation and control of their numbers by indigenous antibacterial factors. Unless this steady state is disrupted, the result is a quiet, healthy mucous membrane surface in which both bacteria and host coexist with certain mutual advantages. For the host, the normal flora provides protection against colonization by organisms of greater virulence and pathogenic potential, thereby becoming part of the eye's defense against infection.[1] The presumed benefits to the normal flora are a habitat and the resources to proliferate.

This stable relationship exists as long as the normal flora does not proliferate beyond its usual numbers or location. Although bacteria are tolerated on the ocular surface, keratitis results if they infiltrate the corneal stroma. However, invasion into the tissue is not an initial prerequisite for infection; with excessive proliferation "normal flora" and its by-products become toxic to the eye. The response to this insult is an inflammatory reaction (conjunctivitis or keratoconjunctivitis), and its successful conclusion returns the ocular flora to a normal balance.

Staphylococcus epidermidis and diphtheroids predominate among the flora isolated from healthy eyes, although species of greater virulence such as *S. aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa,* and even meningococci have been reported.[2,3] It has been suggested that these more virulent species of bacteria are present primarily as transients, and their presence does not represent true colonization of the eye. Even a transient presence represents a source of serious infection, which is especially important in children.[4,5]

Given the proper conditions, virtually any strain of bacteria can cause infection of the conjunctiva or cornea.[6] Even diphtheroids, organisms of extremely low virulence can be found in large numbers in chronic ulceration of the corneal stroma.[7,8] The proper conditions for infection usually involve a breakdown of host defenses (for example, epithelial abrasion), or the introduction of pathogenic organisms in sufficiently large numbers to overwhelm host defenses.

Antibacterial Factors in Eyes

The tear film is a relatively cool and nutrient-poor medium that constantly dilutes and flushes free-floating bacteria from the surface of the eye. Lactoferrin, antibodies, lysozyme, beta-lysins, ceruloplasmin, orosomucoid, and components of the complement system all play a role in the control and elimination of bacteria on the ocular surface.

Bacterial adhesion to the corneal surface is inhibited by the epithelial glycocalyx.[9] The inability of bacteria to adhere to the ocular surface

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increases the effectiveness of the flushing action of tears. The ability of some *Pseudomonas* strains to adhere to undamaged epithelium increases their virulence.[10-12] A breakdown of the glycocalyx barrier results in increased bacterial adhesion and is a primary initiating factor in bacterial keratitis.[13-15] When the epithelium is breached, other humoral and cellular immune defenses must be activated to eliminate the offending organisms.[16,17]

Both local and systemic disorders can undermine these defenses and predispose the cornea to infection. Disorders such as trichiasis, lagophthalmos, and dry eye compromise the ability of the epithelium to maintain an intact barrier. Patients with dry eye have abnormally low levels of lysozyme, poor tear film stability, and reduced tear turnover, all of which lessen ocular surface defenses. Adjacent infections, such as dacryocystitis, can provide a large bacterial reservoir on the corneal and conjunctival surface. Chronic bacterial conjunctivitis usually requires such an adnexal source of bacteria and typically will resolve when this source is eliminated.[18]

Contact lenses induce stasis of the precorneal tear film and provide structure for bacterial adherence and multiplication. With continued wear, contact lens surfaces become progressively modified and are colonized by bacteria. Recent reports suggest that contact lenses are a major contributor to corneal infection, especially among extended-wear contact lens users.[19-21] In cases of bacterial keratitis among contact lens wearers, large numbers of pathogenic bacteria can frequently be cultured from both the contact lenses and from poorly cleaned contact lens cases. Other external sources of infection include contaminated mascara, eye preparations, and topical medications.[22,23]

Microbial keratitis in eyes that have undergone penetrating keratoplasty is usually bacterial[24] and is reported to cause visual loss in 46% of cases.[25] As many as 35% require emergency re-grafting.[26] Loose sutures, chronic corticosteroid use, bandage contact lenses, and chronic epithelial defects all have been identified as contributing factors in these patients.[24-26]

Bacterial Pathogens

Bacterial keratitis and conjunctivitis are commonly caused by the same organisms that have an affinity for the outer eye. Notable exceptions are *P. aeruginosa*, which is a frequent cause of corneal ulceration but rarely found as an isolate in uncomplicated primary conjunctivitis, and *Haemophilus* influenzae, which frequently causes acute conjunctivitis in children but is not usually associated with corneal ulceration. Although climate, regional differences, sanitary conditions, and the nutritional status of patient populations can vary the incidence, most cases of bacterial keratitis are caused by relatively few species (Table). These organisms are manifest worldwide on the surface of the eye, and under the proper conditions are able to overcome ocular defenses against infection.

Bacterial Conjunctivitis

Acute infectious conjunctivitis is often viral in origin. The prevalence of acute forms of bacterial conjunctivitis varies greatly in response to regional, hygienic, social, and climatic factors. Bacterial conjunctivitis is characterized by large numbers of leukocytes in the tear film, with individual cells visible in the tear meniscus on slit-lamp examination. These cells create a purulent or mucopurulent discharge over the caruncle.

For convenience, four types of bacterial conjunctivitis are described on the basis of manifestation, time course, and the initiating factors.[27]

Hyperacute Bacterial Conjunctivitis

Hyperacute bacterial conjunctivitis usually is caused by *Neisseria gonorrhoeae*. Its invasiveness, virulence, and pathogenicity elicit a violent inflammatory response that is characterized by a copious purulent discharge. It progresses rapidly, with edema of the eyelids and conjunctiva, tenderness and aching of the globe, and a prominent periauricular node.[18,28] If left untreated, *N. gonorrhoeae* is capable of penetrating an intact cornea within two days.

Gonococcal conjunctivitis is an oculogenital disease, usually spread to the eye by direct contact with secretions or infected urine, or indirectly via the hands. The predominance of right-eye infections in right-handed males with genital infections suggests the latter route is most common.[27] The presence of a hyperacute conjunctivitis suggests a venereal origin and devastating ocular consequences if the disease is left untreated.

Other, less common, causes of hyperacute conjunctivitis include *N. meningitidis, Branhamella catarrhalis,* and *Acinetobacter calcoaceticus,* all of which can be confused clinically and on the initial Gram stain with *N. gonorrhoeae.*[28]

A clinical conjunctivitis may be produced by *N. meningitidis* that is identical to that of *N. gonorrhoeae* but typically has a milder course with less corneal involvement. This conjunctivitis occurs primarily in children and has been shown to be the probable source of systemic meningococcal disease in six of 21 patients with primary meningococcal conjunctivitis.[4]

All cases of hyperacute conjunctivitis should have initial Giesma and Gram stain performed on conjunctival scrapings. Cultures taken directly from the eye should be inoculated onto Thayer-Martin and chocolate agar with appropriate fermentation tests and antibacterial sensitivities performed. It has been suggested that, in children, any hyperacute or acute purulent conjunctivitis should be cultured and a Gram stain performed. If the Gram stain discloses gram-negative diplococci, initial therapy should include both systemic and topical antibiotic therapy.[4]

TABLE
REGIONAL DIFFERENCES IN PATHOGENS MOST COMMONLY ISOLATED FROM BACTERIAL KERATITIS

COUNTRY	MOST COMMON BACTERIA	NO.	%	TOTAL CASES
U.S.A.				
New York[36]	*S. aureus*	163	33	
	S. epidermidis	79	16	
	Moraxella sp.	79	16	494
Southern Florida[48]	*Pseudomonas* sp.	74	31	
	S. aureus	51	21	
	S. epidermidis	19	8	238
India[56]	*S. aureus*	144	40	
	S. epidermidis	97	27	
	P. aeruginosa	89	25	355
Kuwait[47]	*S. epidermidis*	100	64	
	S. aureus	19	12	
	P. aeruginosa	12	7	156
Nepal[40]	*St. pneumoniae*	124	31	
	S. epidermidis	37	12	
	S. aureus	35	11	324
South Africa[41]	*St. pneumoniae*	21	40	
	P. aeruginosa	9	17	
	S. epidermidis	4	8	53
Bangladesh[57]	*P. aeruginosa*	8	30	
	S. aureus	6	22	
	Proteus sp.	2	8	40

Acute Bacterial Conjunctivitis

Acute bacterial conjunctivitis usually manifests as a vague foreign body sensation and tearing, followed by a modest mucopurulent discharge and diffuse conjunctival hyperemia in one eye. If uninvolved initially, the fellow eye is frequently infected within two days. The creamy mucopurulent discharge accumulates in the nasal palpebral fissure and on the cilia and eyelid margins. Upon awakening, it gives rise to the complaint that the eyelids are stuck together. A superficial epithelial punctate keratitis generally is manifest during the first few days of infection and tends to resolve spontaneously. One to 2 mm of blepharoptosis with mild swelling and erythema of the eyelid is common.

Because of the noninvasive nature of the infection, most bacteria and their by-products are primarily discharged from the ocular surface through the nasolacrimal drainage system, not through lymphatic drainage. Therefore, in cases of acute bacterial conjunctivitis, the tender preauricular lymph node accompanying viral and invasive infections is usually small or absent.

Bacterial colonization of the conjunctival surface is facilitated by the microorganism's ability to adhere to and proliferate on soft contact lenses. As a result, many patients with acute bacterial conjunctivitis are young adults who fail to follow the recommendations for care of their contact lenses.

Many cases of acute bacterial conjunctivitis may be self-limited and may resolve without treatment. However, topical treatment with antibiotics is recommended because it shortens the course of the disease, reduces the incidence of permanent conjunctival changes, and decreases the potential for corneal ulceration or systemic infection.

A common, worldwide cause of conjunctivitis is *S. aureus,* which affects all age groups. The acute form may resolve spontaneously or progress to a chronic infection. Clinical features such as sterile, peripheral corneal infiltrates, phlyctenulosis, and limbal nodules may evolve; they reflect the tenacious growth characteristics of *S. aureus* and their ability to produce various toxins and enzymes.

Haemophilus influenzae is a cause of acute conjunctivitis in children. Small conjunctival petechial hemorrhages and marginal corneal infiltrates occur early. The untreated infection may resolve within 15 days. However, the more virulent strains of *Haemophilus* such as *H. influ-*

enzae type B can cause severe systemic disease, meningitis, and preseptal cellulitis, particularly in children under 4 years of age.

Acute pneumococcal conjunctivitis also occurs primarily in children and may be associated with petechial conjunctival hemorrhages. The untreated infection may resolve in seven to ten days without scarring but is rarely allowed to progress without treatment.

Neonatal Conjunctivitis

This form of acute or hyperacute conjunctivitis usually manifests within the first few days after birth. The importance of conjunctivitis in neonates cannot be overemphasized. Any of the bacteria causing conjunctivitis, especially in the immunologically immature, premature infant, can produce sepsis and a lethal outcome. Prompt diagnosis by Gram stain and culture may be lifesaving.[29]

Numerous bacteria cause neonatal conjunctivitis with the potential for secondary meningitis, cellulitis, and septicemia.[30] These include *Escherichia coli, S. aureus,* and *H. influenzae.* However, the most virulent form of neonatal conjunctivitis is the hyperacute purulent conjunctivitis caused by *N. gonorrhoeae.* Almost one million cases of gonorrhea are reported annually to the Centers for Disease Control. The current incidence of neonatal infection is 0.6%.[31,32] Credé prophylaxis of the conjunctiva with topically applied silver nitrate has dramatically curtailed the damage this organism had inflicted in the past, but the organism has proven to be exceedingly difficult to eradicate.[28,32,33] Untreated, this hyperacute purulent conjunctivitis can rapidly progress to corneal ulceration and perforation. The clinical manifestation and time of onset of this and the other causes of neonatal conjunctivitis can be variable, and laboratory diagnostic studies are always necessary for their evaluation and treatment.[18]

Chronic Bacterial Conjunctivitis

The most common cause of chronic bacterial conjunctivitis is *S. aureus,* largely because of its ability to establish and maintain growth on the eyelid and in associated glands. It has been cultured from the conjunctiva of 12% of healthy eyes, and from the eyelid margins of more than 33% of healthy eyes.[3,34] Many authors do not consider *S. aureus* to be a part of the eye's "normal flora," although exceptions occur.[35] This may simply belie the relatively frequent occurrence of *S. aureus* infections and their wide range of severity. For example, colonization of the eyelid margin and conjunctiva by *S. aureus* may produce subclinical signs in an otherwise healthy eye. However, the same number of bacteria in a patient with keratoconjunctivitis sicca would be much more likely to result in a clinically active infection.

The distinction between the presence of *S. aureus* as part of the normal ocular flora or as a pathogen is relevant. Cases of asymptomatic colonization have apparently not been treated in large studies, implying tolerance to its presence.[3,36] Nonetheless, the pathogenic potential of this opportunistic organism must be respected, and in its presence, maintenance of good eyelid hygiene is prudent. Many physicians elect to treat *S. aureus,* whenever it is cultured, topically with antibiotics but the long-term efficacy of this approach for preventing bacterial re-establishment is unknown. Long-term eradication of *S. aureus* may indeed not be possible in some eyes.

A wide range of clinical signs accompany *S. aureus* infection because of the different toxins it produces and variable host responses. Superficial punctate keratopathy commonly involves the lower one third of the cornea. Marginal peripheral catarrhal ulcers are presumed to be an immune response. These are differentiated from the limbal infiltrates of acute *H. influenzae* by a clear zone between the infiltrate and the corneoscleral limbus. They may coalesce to form a ring infiltrate but generally do not lead to thinning or perforation. Other findings include the presence of conjunctival and corneal phlyctenules, gelatinous nodules also thought to be caused by immune phenomena. They regress with topical corticosteroid treatment but may leave scars.

Long-term infection can result in eyelid disorders such as trichiasis, poliosis, madarosis, ulcerative blepharitis, marginal telangiectasia, hordeola, chalazia, and chronic meibomitis. Dermatonecrotoxin can cause a periorbital inflammatory dermatitis not unlike a mild atopic reaction. Because of its prevalence, *S. aureus* has been reported to be a more common cause of angular blepharitis than *Moraxella* species.[17]

Moraxella species are frequently part of the nasopharyngeal flora in alcoholic and debilitated patients,[37] and often play a role in opportunistic ocular infection. They are reported to be more common in warmer climates and usually manifest as a chronic follicular conjunctivitis.

This form of conjunctivitis may be associated with the breakdown of the temporal canthal epidermis, commonly referred to as angular blepharitis.

Bacterial Keratitis

The diagnostic and therapeutic tools available to ophthalmologists have advanced tremendously since the first demonstration of the infectious nature of purulent urethral discharge by the inoculation of blind human eyes.[38] Despite such tools, bacterial corneal ulceration remains a major cause of blinding disease, both in developed countries and in countries where trachoma and vitamin deficiency states are endemic.[39]

In developing countries, corneal trauma is the primary initiating factor in the development of corneal ulceration[40,41]; in industrialized nations contact lens complications are the most common cause,[39,42] with eyelid disease and tear film abnormalities being important associated factors worldwide.[36] In undeveloped countries, the prevalence of bacterial corneal ulceration after corneal trauma among rural agricultural laborers makes alteration of these epidemiologic patterns unlikely. Even relatively minor infections in the visual axis can cause a serious loss of vision, and severe infections can penetrate the cornea with loss of the eye within 24 hours.[43] Therefore, every corneal ulcer is an emergency. Rapid identification of the responsible organism by culture, followed by antibiotic treatment, is imperative for a successful outcome.

The most common bacterial causes of corneal ulceration vary in different regions of the world (Table). The lack of documentation of these variations has hampered treatment in many areas. *Streptococcus pneumoniae* is the most commonly isolated pathogen in many developing countries, in contrast to its decreasing frequency in recent series from North America.[36,40,41,44-46] First-line treatment of corneal ulceration with aminoglycoside antibiotics is inappropriate in a country where *S. pneumoniae* is the predominant pathogen.[40]

The predominance of *S. epidermidis* and the lack of fungal keratitis in 228 patients from the nonagricultural desert environment of Kuwait contrasts with the prevalence of agricultural corneal trauma as a cause of ulceration (53% of ulcers from Nepal), and the prevalence of fungal keratitis (20% incidence) in South Florida.[40,47,48] Regional variations within the United States reflect different patient populations and climatic effects. Gram-positive keratitis predominates in much of this country, but in South Florida, *Pseudomonas* infections have been reported in 31% to 49% of cases.[48] Fungal infections also are more common in the southern part of the United States than nationwide. Males are more commonly affected in most areas.[36,48]

Pathogenesis

Fortunately, most bacteria are unable to break down or adhere to the epithelial glycocalyx unless it is damaged. Exceptions include *N. gonorrhoeae, H. aegyptius, Corynebacterium diphtheriae,* and *Listeria* sp.; all are capable of penetrating healthy, intact epithelium.[17] Although the majority of epithelial abrasions heal without incident, breakdown of the epithelial protective barriers allows any opportunistic bacteria present to infect the cornea.

Bacteria multiply and spread within the stroma, often releasing enzymes and toxins. The body's primary defense against bacterial invasion of the cornea is the polymorphonuclear leukocyte. In response to bacterial and endogenous chemotactic factors, polymorphonuclear leukocytes enter the cornea and phagocytize bacteria. Digestion and killing of bacteria occur inside lysosomes, structures located in the cytoplasm of the polymorphonuclear leukocyte, and involve numerous enzymes, including proteoglycanase, elastase, cathepsins, lysozyme, and myeloperoxidase as well as the oxidative burst phenomena.[49] Both the bacterial and the leukocytic enzymes are poorly tolerated by the components of the avascular stroma. These enzymes are capable of proteoglycan and collagen breakdown; they destroy the stroma and are responsible for stromal necrosis and corneal thinning and for the scar that results from the repair of this damage.[50,51] Polymorphonuclear leukocyte enzymes are the primary enzymes responsible for collagen damage in models of *P. aeruginosa* keratitis, and they may be responsible for the loss of epithelium around these ulcers.[50,52,17]

Clinical Features

The classical features of bacterial keratitis include decreased visual acuity, photophobia, purulent discharge, tearing, and redness in a previously healthy eye after trauma or contact lens wear. Examination discloses an opaque, generally round, stromal infiltrate, usually devoid of epithelium and often with exudate and mucus adherent to its surface. An anterior chamber flare and cell response almost invariably are present. Fibrin in the aqueous humor, hypopyon, keratic precipitates, and other deposits on the corneal endothelium as well as a constricted pupil are common. Stromal and epithelial edema with folds at the level of Descemet's membrane are typical, and nonspecific conjunctivitis is invariably manifest. More severe and long-standing infections can be complicated by peripheral anterior synechiae, secondary glaucoma, and hyphema.

None of the clinical signs or symptoms allow reliable microbiologic diagnosis. Classification according to their clinical features is of limited use. Initial treatment consists of broad spectrum antibiotics based on known pathogens and their antibiotic sensitivities in a given region.[53] Species-specific antibiotic coverage before the availability of culture and sensitivity results is unreliable. There is great potential for misidentification of organisms with staining techniques when only a single causal organism is involved. This problem is further compounded because 6% to 18% of ulcers are infected with multiple organisms.[17,53,54]

Laboratory Diagnosis

Despite the development of sophisticated assays for the presence of bacteria, little has changed during the past decade in the routine identification of organisms responsible for bacterial conjunctivitis and keratitis. In the case of bacterial keratitis it is important that every ulcer be cultured and receive a full laboratory evaluation. Atypical case histories or manifestations may require the use of additional media or stains, but an established routine that includes an organized corneal tray and a laboratory familiar with the routine will avoid delay in the treatment of multiorganism or unresponsive cases. Recovery of bacteria on culture media after antibiotic therapy has been initiated is difficult, even in the face of worsening infection. Prior antibiotic treatment also can alter the staining characteristics of many bacteria.[17] Cultures should be taken before any antibiotic is instilled. Indolent or healing ulcers that suddenly deteriorate should receive another complete work up, as the condition may reflect a secondary infection with a new organism. Detailed staining and culturing techniques have been described elsewhere.[55]

In conclusion, bacterial infection of the corneal stroma is an opportunistic infection that occurs primarily after trauma to the epithelium. The principal causal organisms vary in different climatic regions. Rapid diagnosis and treatment are essential to minimize corneal scarring and visual loss. Acute bacterial conjunctivitis usually is a less severe infection, except in neonates and young children, where careful observation and prompt treatment, including systemically administered antibiotics, may be required to prevent systemic dissemination.

References

1. Okumoto, M.: Normal flora in the defense of the conjunctiva against infection. In O'Connor, G. R. (ed.): Immunologic Diseases of the Mucous Membranes. Pathology, Diagnosis and Treatment. New York, Masson et Cie, 1980, Chap. 5.
2. Cagle, G. D., and Abshire, R. L.: Quantitative ocular bacteriology. A method for the enumeration and identification of bacteria from the skin-lash margin and conjunctiva. Invest. Ophthalmol. Vis. Sci. 20:751, 1981.
3. Perkins, R. E., Kundsin, R. B., Pratt, M. V., Abrahamsen, I., and Leibowitz, H. M.: Bacteriology of normal and infected conjunctiva. J. Clin. Microbiol. 1:147, 1975.
4. Moraga, F. A., Domingo, P., Barquet, N., Gasser, I., and Gallart, A.: Invasive meningococcal conjunctivitis. J.A.M.A. 264:333, 1990.
5. Burns, R. P., and Rhodes, D. M.: *Pseudomonas* eye infection as a cause of death in premature infants. Arch. Ophthalmol. 65:517, 1961.
6. Webb, R. M., and Tabbara, K. F.: Indolent bacterial corneal ulcers. Cornea 1:337, 1982.
7. Rubinfeld, R. S., Cohen, E. J., Arensten, J. J., and Laibson, P. R.: Diphtheroids as ocular pathogens. Am. J. Ophthalmol. 108:251, 1989.
8. Heidemann, D. G., Dunn, S. P., Diskin, J. A., and Aiken, T. B.: *Corynebacterium striatus* keratitis. Cornea 10:81, 1991.

9. Reed, W. P., and Williams, R. C.: Bacterial adherence. First step in pathogenesis of certain infections. J. Chronic Dis. 31:67, 1978.

10. Davis, S. D., Kushnaryov, V. M., and Hyndiuk, R. A.: Role of pili in virulence of *Pseudomonas aeruginosa* for scratched rabbit cornea. Presented at the Ocular Microbiology and Immunology Group Meeting. Chicago, Nov. 4, 1983.

11. Stern, G. A., Lubniewski, A., and Allen, C.: The interaction between *Pseudomonas aeruginosa* and the corneal epithelium. Arch. Ophthalmol. 103:1221, 1985.

12. Ramphal, R., McNiece, M. T., and Polack, F. M.: Adherence of *Pseudomonas aeruginosa* to the injured cornea. A step in the pathogenesis of corneal infections. Ann. Ophthalmol. 13:421, 1981.

13. Ostler, H. B., Thygeson, P., and Okumoto, M.: Infectious diseases of the eye. III. Infections of the cornea. J. Contin. Ed. Ophthalmol. 40:11, 1978.

14. Kelinske, M., and Poirier, R.: Corneal ulceration due to *Shigella flexneri*. J. Pediatr. Ophthalmol. Strabismus 17:48, 1980.

15. Meurs, P. J., and Van Bijsterveld, O. P.: *Nocardia gypsoides* corneal ulcer. Br. J. Ophthalmol. 68:179, 1984.

16. Tragakis, M., Economidis, I., and Pollalis, S.: Tear immunoglobulin levels in normal persons and patients with staphylococcal, trachomatous and allergic disease. In Trevor-Roper, P.D. (ed): 6th Congress of the European Society of Ophthalmology. New York, Grune and Stratton, 1980, p. 281.

17. Hyndiuk, R. A., Nassif, K. F., and Burd, E. M.: Bacterial diseases. In Smolin, G., and Toft, R. A. (eds.): The Cornea. Scientific Foundations and Clinical Practice. Boston, Little, Brown, and Company, 1983, p. 147.

18. Mannis, M. J.: Bacterial conjunctivitis. In Kaufman, H. E., McDonald, M. B., Barron, B. A., and Waltman, S. R. (eds.): The Cornea. Boston, Little, Brown, and Company, 1988, p. 189.

19. Ormerod, L. D., Murphree, A. L., Gomez, D. S., Schanzlin, D. J., and Smith, R. E.: Microbial keratitis in children. Ophthalmology 93:449, 1986.

20. Schein, O. D., Glynn, R. J., Poggio, E. C., Seddon, J. M., Kenyon, K. R., and the Microbial Keratitis Study Group: The relative risk of ulcerative keratitis among users of daily-wear and extended wear soft contact lenses. A case-control study. N. Engl. J. Med. 321:773, 1989.

21. Lemp, M. A., Blackman, H. J., and Wilson, L. A.: Gram-negative corneal ulcers in aphakic eyes with extended wear contact lenses. Ophthalmology 90:60, 1984.

22. Grayson, M.: Keratitis. In Grayson, M. (ed.): Diseases of the Cornea, ed. 2. St. Louis, C. V. Mosby, 1983, p. 56.

23. Wilson, L. A., and Ahern, D. G.: *Pseudomonas*-induced corneal ulcers associated with contaminated eye mascaras. Am. J. Ophthalmol. 84:112, 1977.

24. Fong, L. P., Ormerod, L. D., Kenyon, K. R., and Foster, C. S.: Microbial keratitis complicating penetrating keratoplasty. Ophthalmology 95:1269, 1988.

25. Tuberville, A. W., and Wood, T. O.: Corneal ulcers in corneal transplants. Curr. Eye Res. 1:479, 1981.

26. Harris, D. J., Stulting, R. D., Waring, G. O., and Wilson, L. A.: Late bacterial and fungal keratitis after corneal transplantation. Spectrum of pathogens, graft survival, and visual prognosis. Ophthalmology 94:1450, 1988.

27. Wilson, L. A.: Bacterial conjunctivitis. In Duane, T. D. (ed.): Clinical Ophthalmology, vol. 4. Philadelphia, Harper & Row, 1984, p. 1.

28. Ullman, S., Roussel, T. J., and Forster, R. K.: Gonococcal keratoconjunctivitis. Surv. Ophthalmol. 32:199, 1987.

29. Johnson, D., and McKenna, H.: Bacteria in ophthalmia neonatorum. Pathology 7:199, 1975.

30. Prentice, M. J., Hutchinson, G. R., and Taylor-Robinson, D.: A microbiological study of neonatal conjunctivae and conjunctivitis. Br. J. Ophthalmol. 61:601, 1977.

31. Centers for Disease Control: Table 1 Summary-Cases Specified Notifiable Diseases. United States. MMWR 35:810, 1987.

32. Rothenberg, R.: Ophthalmia neonatorum to *Neisseria gonorrhoeae*. Sex. Transm. Dis. 6(suppl. 2):187, 1979.

33. American Academy of Pediatrics. Prophylaxis and treatment of neonatal gonococcal infections. Pediatrics 65:1047, 1980.

34. Baum, J. L.: Ocular infections. N. Engl. J. Med. 299:28, 1978.

35. Barza, M., and Baum, J.: Ocular infections. Med. Clin. North Am. 67:131, 1983.

36. Asbell, P., and Stenson, S.: Ulcerative keratitis. Survey of thirty years laboratory experience. Arch. Ophthalmol. 100:77, 1982.

37. Baum, J., Fedukowicz, H. B., and Jordan, A.: A survey of *Moraxella* corneal ulcers in a derelict population. Am. J. Ophthalmol. 90:476, 1980.

38. Duke-Elder, S., and Leigh, A. G.: Diseases of the Outer Eye. Cornea and Sclera. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 8., pt. 2. St. Louis, C. V. Mosby, 1965.

39. Whitcher, J. P.: Corneal ulceration. Int. Ophthalmol. Clin. 30:30, 1990.

40. Upadhyay, M. P., Karmacharya, P. C. D., and Koirala, S.: Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal. Am. J. Ophthalmol. 111:92, 1991.

41. Carmichael, T. R., Wolpert, M., and Koornhof, H. J.: Corneal ulceration at an urban African hospital. Br. J. Ophthalmol. 69:920, 1985.

42. Schein, O. D., Ormerod, L. D., Barraquer, E., Alfonso, E., Egan, K. M., Paton, B. G., and Kenyon, K. R.: Microbiology of contact lenses-related keratitis. Cornea 8:281, 1989.

43. Fedukowicz, H. B.: External Infections of the Eye. New York, Appleton-Century-Crofts, 1978, p. 171.

44. Thygeson, P.: Acute central ulcers of the cornea. Calif. Med. 69:18, 1948.

45. Pahalkar, S., Thomas, A., and Alexander, T. A.: Bacterial and mycotic agents of corneal ulcers in Vellore. Ind. J. Ophthalmol. 3:289, 1985.

46. Chaudhuri, P. R., and Godfrey, B.: Treatment of bacterial corneal ulcers with concentrated antibiotic eyedrops. Trans. Ophthalmol. Soc. U.K. 102:11, 1982.

47. Al-Samarrai, A. R., and Sunba, M. S. N.: Bacterial corneal ulcers among Arabs in Kuwait. Ophthalmic Res. 21:278, 1989.

48. Liesegang, T. J., and Forster, R. K.: Spectrum of microbial keratitis in South Florida. Am. J. Ophthalmol. 90:38, 1980.

49. Babior, B. M.: Oxygen dependent microbial killing by phagocytes. N. Engl. J. Med. 298:721, 1978.

50. Van Horn, D. L., Schultz, R. O., and Kwasny, G. P.: *Pseudomonas* corneal ulceration. An electron microscopic study. Ann. Ophthalmol. 3:203, 1958.

51. Twining, S. S., Hatchell, D. L., and Hyndiuk, R. A.: Acid proteases and histopathologic correlations in experimental ulceration in vitamin A deficient rabbit corneas. Invest. Ophthalmol. Vis. Sci. 26:31, 1985.

52. Hyndiuk, R. A.: Experimental *Pseudomonas* keratitis. Trans. Am. Ophthalmol. Soc. 79:541, 1982.

53. Baum, J. L.: Initial therapy of suspected microbial corneal ulcers. I. Broad antibiotic therapy based on prevalence of organisms. Surv. Ophthalmol. 24:97, 1979.

54. Leibowitz, H. M.: Bacterial keratitis. In Corneal Disorders. Clinical Diagnosis and Management. Philadelphia, W. B. Saunders, 1984, p. 353.

55. Jones, D. B., Liesegang, T. J., and Robinson, N. M.: Cumitech 13. Laboratory diagnosis of ocular infections. Washington, D.C., American Society for Microbiology, 1981.

56. Mahajan, V. M.: Ulcerative keratitis. An analysis of laboratory data in 674 cases. J. Ocul. Therap. Surg. 4:138, 1985.

57. Katz, N., Wadud, S., and Ayazuddid, M.: Corneal ulcer disease in Bangladesh. Ann. Ophthalmol. 15:834, 1983.

Current Therapy for Bacterial Keratitis and Bacterial Conjunctivitis

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Therapy of bacterial keratitis and conjunctivitis requires that antibiotics be administered to eliminate viable bacteria. Only a limited number of ophthalmic antibiotics are commercially available. Although generally adequate for the treatment of bacterial conjunctivitis, the commercial preparations are believed to contain too low a concentration of antibiotic for the treatment of bacterial keratitis. Using products designed for parenteral administration, the ophthalmologist or the pharmacist formulates so-called fortified preparations containing much higher antibiotic concentrations. Because of their limited spectrum of action, two fortified preparations generally are administered concurrently. Topical application is the most effective route of antibiotic administration for treatment of bacterial keratitis. Antibiotics may also be injected periocularly, a method with risk, or intravenously, a method of uncertain efficacy.

BACTERIAL KERATITIS and severe bacterial conjunctivitis require immediate therapy with an effective antimicrobial agent. Since the specific etiologic organism and its antibiotic susceptibility are not known initially, an agent with broad antibacterial coverage is needed. Many such infections are associated with a disturbance of the normal anatomy or physiology of the eyelids, lacrimal system, conjunctiva, or cornea that results in a breakdown of host defenses and allows infectious bacteria to invade and colonize the tissue. For example, a minor abrasion of the corneal epithelium caused by a contact lens, misdirected lashes, or a foreign body provides an opportunity for bacterial invasion of the corneal stroma.

The primary pathogens associated with bacterial keratitis in the United States include *Staphylococcus*, *Pseudomonas*, *Streptococcus*, and gram-negative enteric organisms.[1] The pathogens most often associated with bacterial conjunctivitis are *S. aureus*, *S. epidermidis*, and a variety of other gram-positive and gram-negative bacteria.[2] In the pediatric age group, *Haemophilus influenzae* and *St. pneumoniae* are frequently identified causes of conjunctivitis.

Topical Ophthalmic Antibiotics

Most cases of bacterial keratitis and bacterial conjunctivitis are treated with topically applied antibiotics. A number of topical ophthalmic agents are available; their properties, including their range of antibacterial activity and effectiveness in vivo, vary considerably.

Erythromycin

Erythromycin, available as a 0.5% ophthalmic ointment, inhibits protein synthesis by bacterial ribosomes. The drug is bacteriostatic (possibly bactericidal in high concentrations) and is primarily effective against gram-positive organisms. Gram-negative coverage is limited to *Neisseria gonorrhoeae*, *N. meningitidis*, and *H. influenzae*. Because of its bacteriostatic mechanism of action and the inability to prepare a concentrated formulation, erythromycin is rarely used to treat serious cases of bacterial keratitis. Nonetheless, it is a useful drug for the treatment of bacterial conjunctivitis. However, strains of *S. aureus*, *St. pneumoniae*, and *St. pyogenes* resistant to erythromycin are said to be increasing.

Aminoglycosides

Two commercially available topical ophthalmic aminoglycosides, gentamicin, and tobra-

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mycin, are widely used to treat bacterial keratitis and conjunctivitis. Both drugs are available as a 0.3% solution and ointment, a concentration suitable for treatment of bacterial conjunctivitis. Most authorities recommend that a 1.4% solution of these agents be formulated to treat bacterial keratitis.

The aminoglycosides inhibit bacterial protein synthesis by altering bacterial ribosomes. Their antibacterial spectrum of activity and their clinical effectiveness are similar. They are highly effective against gram-negative bacilli including *P. aeruginosa.* In vitro, tobramycin is more active than gentamicin against *P. aeruginosa.* Gentamicin and tobramycin are considerably less effective against gram-negative cocci, such as *Neisseria* and *Haemophilus* organisms, and should not be used as primary therapy for a keratitis caused by these organisms. Tobramycin and, to a lesser extent, gentamicin are effective against most strains of staphylococci encountered in the external eye. Aminoglycosides are not suitable antibiotics for treatment of streptococcal (including *St. pneumoniae*) keratitis since their minimal inhibitory concentration for these pathogens is often more than 100 times higher than bacitracin or erythromycin.[3]

Bacitracin

Bacitracin is a bactericidal antibiotic that inhibits bacterial cell wall synthesis. For ophthalmic use it is commercially available only in ointment form at a concentration of 500 units/g, which is useful for treatment of bacterial conjunctivitis. For treatment of bacterial keratitis, a fortified eyedrop is prepared at a concentration of 10,000 units/ml. Bacitracin's spectrum of action is limited to gram-positive organisms. It is particularly useful for treatment of staphylococcal and streptococcal infections. Bacitracin is not used systemically so that resistant strains of these organisms are less likely to be encountered.

Polymyxin B

Polymyxin B is a bactericidal antibiotic that binds to and damages the bacterial cell membrane, rendering it ineffective as a semipermeable osmotic barrier. It is not commercially available as a single entity for ophthalmic use. When required to treat bacterial keratitis, it is reconstituted from a sterile powder into a fortified solution at concentrations as high as 25,000 units/ml. The spectrum of action of polymyxin B is confined to gram-negative bacilli. Its use has been almost entirely superseded by the aminoglycosides.

Chloramphenicol

Chloramphenicol is a broad-spectrum synthetic antibiotic available for ophthalmic use as a 0.5% solution and a 1.0% ointment. It is a potent inhibitor of bacterial protein synthesis and is generally classified as a bacteriostatic agent. Experimental data derived after topical ophthalmic application suggest that it may function as a bactericidal agent against susceptible organisms infecting the cornea.[4] Chloramphenicol is active against a wide variety of gram-positive and gram-negative bacteria. However, its topical ophthalmic application has apparently been associated with cases of fatal aplastic anemia, and this has understandably markedly limited its use.

Sodium Sulfacetamide

Sodium sulfacetamide is not an antibiotic but is widely used to treat mild infections of the external eye. It is a bacteriostatic antimicrobial agent that inhibits bacterial metabolism and is most commonly marketed in solution and ointment forms at a concentration of 10%, although concentrations as high as 30% have been commercially available. Many gram-positive and gram-negative bacteria are susceptible to sodium sulfacetamide, but only weakly so, and common ocular pathogens, such as *S. aureus,* have become increasingly resistant. Use of sodium sulfacetamide is confined to the less severe forms of conjunctivitis; it has no place in the treatment of bacterial keratitis.

Antibiotics Formulated For Topical Ophthalmic Use

The following antibiotics are not commercially available as ophthalmic products. However, at times, each may be administered topically to treat serious bacterial infections of the cornea. High concentration ophthalmic solutions are prepared from products for parenteral use, as required, by the ophthalmologist or the local pharmacy.

Cephalosporin

Cephalosporins are bactericidal antibiotics that inhibit bacterial cell wall synthesis. First-generation cephalosporins, particularly cefazolin, are commonly used to eradicate gram-positive cocci and bacilli. Many *Neisseria* organisms also are susceptible to this antibiotic.

Vancomycin

Vancomycin hydrochloride is a bactericidal antibiotic that interferes with the synthesis of bacterial cell walls and inhibits the growth of spheroplasts. Its spectrum of action is limited to gram-positive organisms; it is highly effective against staphylococcal and streptococcal species. Its use is often reserved for cases of staphylococcal or streptococcal keratitis resistant to other antibiotics.

Amikacin

Amikacin sulfate is a bactericidal aminoglycoside that interferes with the synthesis of bacterial cell walls. Its spectrum of action resembles that of gentamicin and tobramycin. However, it is often effective against an organism that is resistant to these first-line aminoglycosides, and its use for the treatment of bacterial keratitis is reserved for this purpose.

Ticarcillin

Ticarcillin disodium is a bactericidal penicillin derivative that inhibits bacterial cell wall synthesis. It is less effective against gram-positive organisms than the earlier generation of penicillins. However, it is effective against *P. aeruginosa*, and its use in the treatment of bacterial keratitis is limited to this organism. Since *P. aeruginosa* organisms rapidly become resistant to this agent if used alone, it is always administered in conjunction with a second antibiotic, generally an aminoglycoside, to provide a synergistic effect.

Combination Products

To compensate for the limited range of antibacterial activity of many ophthalmic antibiotics and for the relatively low potency of commercially available ophthalmic products, the practice of combining two or more antimicrobials has developed. Polypharmacy formulations may include any number of active ingredients; agents frequently used include neomycin, bacitracin, and polymyxin B. These agents have been useful for treatment of bacterial conjunctivitis but are rarely used to treat bacterial keratitis. They are more apt to induce a hypersensitivity reaction, particularly those containing neomycin, than single antimicrobial agents.

A recently introduced product in this class combines trimethoprim sulfate with polymyxin B sulfate. Trimethoprim is active against aerobic gram-positive bacteria, including many strains of staphylococci and streptococci, whereas polymyxin B is active against a wide variety of gram-negative organisms. As with other combination products, this agent is useful for treating conjunctivitis but has no role in the therapy of bacterial keratitis.

Modes Of Antibiotic Administration

Most cases of bacterial conjunctivitis are treated by topical instillation of antibiotics in commercially available concentrations. In the most severe of cases, such as those caused by *Neisseria* species, systemically administered antibiotics are used in conjunction with topical therapy.

Similarly, topical antibiotic administration is the primary mode of therapy for bacterial keratitis. However, the practice of formulating antibiotic agents at higher concentrations than are available commercially in order to obtain higher drug levels in the cornea is widely accepted. Nonetheless, this practice of fortifying ophthalmic antibiotic solutions has never been formally evaluated, and no safety regulations have been established. Hypersensitivity reactions are encountered, especially in a small number of penicillin-sensitive patients who react to cephalosporin, and in some patients receiving aminoglycosides.[5] It is not known if this occurs significantly more often after instillation of fortified preparations than after the application of commercially available products.

In addition to bacitracin, gentamicin, and tobramycin, antibiotics commonly formulated as fortified ophthalmic preparations for treatment of bacterial keratitis include cephalosporin, vancomycin, amikacin and ticarcillin. However, none of the latter group are commercially available as ophthalmic products; they are prepared from products available for parenteral administration.

Under certain circumstances, primarily resistance to treatment with topical fortified antibiotics, the ophthalmologist may concurrently inject antibiotics subconjunctivally or beneath Tenon's capsule in an effort to increase further the antibiotic level in the cornea. Intravenous preparations of gentamicin, tobramycin, and cephalosporin are commonly used for this purpose. However, periocular antibiotic injection has some risk. In some cases, aminoglycoside has leaked into open corneoscleral wounds, resulting in pronounced retinal toxicity with reduced or lost vision.[6,7] Other problems associated with periocular injections include pain, mydriasis, corneal endothelial changes, corneal edema, corneal opacities, conjunctival sloughing/necrosis, subconjunctival hemorrhage, intraretinal hemorrhage, and tissue destruction.[5-13]

Occasionally, systemic administration of antibiotics may be part of the therapeutic regimen for bacterial keratitis. In most instances, this is an admission that topically administered and periocularly injected antibiotics are ineffective. The treatment of corneal infections with systemic therapy, primarily by intravenous injection, carries the risk of systemic toxicity without any evidence that this route of administration contributes a significant antibiotic level to the cornea. Topical administration is by far the most effective delivery method for treating patients with bacterial keratitis. It provides high levels of drug to the site of infection with minimal toxic effects to other parts of the body.

Future Therapy for Bacterial Keratitis and Conjunctivitis

Major disadvantages associated with available antibiotics are low potency and an often narrow range of antimicrobial activity. Moreover, organisms commonly associated with bacterial corneal ulcer are increasingly resistant to standard therapy. Between 8% and 10% of the ulcerative keratitis caused by *P. aeruginosa* are resistant to aminoglycosides.[5] Resistance to aminoglycosides among gram-positive organisms associated with ocular infections is growing at an even faster rate.[5]

The new fluoroquinolones appear to offer an excellent therapeutic option. In vitro studies comparing the effectiveness of fluoroquinolones to that of gentamicin, tobramycin, chloramphenicol, and polymyxin B against bacteria isolated from ocular sources found the fluoroquinolones to be equal and often superior to gentamicin.[14] Studies of fluoroquinolones, including ciprofloxacin, show this new agent to be highly effective against a broad spectrum of gram-positive and gram-negative organisms. In vitro studies showed that ciprofloxacin 0.3% solution killed bacteria at one to four times the minimal inhibitory concentration.[15] Findings involving animal models confirmed that ciprofloxacin was highly active against ocular pathogens, including *P. aeruginosa*.[16]

In clinical studies reported elsewhere in this issue, ciprofloxacin 0.3% ophthalmic solution was found to be effective in more than 90% of patients with bacterial corneal ulcers.[17] Furthermore, no serious side effects attributed to topical application of ciprofloxacin were reported.[17]

The mechanism by which ciprofloxacin inhibits bacteria suggests that resistance will be slow to emerge. By blocking enzymatic activity of bacterial DNA gyrase, ciprofloxacin alters the structure and functioning ability of bacterial DNA. Resistant strains have been achieved only in the laboratory, and then infrequently. Clinical resistance is unlikely since bacteria must undergo two independent chromosomal mutations.[15]

Most encouraging is that, in clinical trials of bacterial corneal ulcers, patients on a regimen of ciprofloxacin administered topically generally improved and ultimately were cured in a shorter period of time than patients given other antibiotics.[17] This speedy effectiveness contributes not only to patient well-being but also to cost containment. Ciprofloxacin 0.3% solution is stable at room temperature, commercially prepared, and distributed through pharmacies. The ophthalmologist has the therapeutic option of a single, potent, broad-spectrum agent that is generally available. Use of ciprofloxacin should be restricted to infectious keratitis or severe bacterial conjunctivitis. Its broad spectrum and high potency make it an excellent choice of first-line therapy while waiting for culture results.

References

1. Leibowitz, H. M.: Bacterial keratitis. In Leibowitz, H. M. (ed.): Corneal Disorders. Clinical Diagnosis and Management. Philadelphia, W. B. Saunders Co., 1984, pp. 356–364.
2. ———: Differential diagnosis of superficial punctate keratopathy. In Leibowitz, H. M. (ed.): Corneal Disorders. Clinical Diagnosis and Management. Philadelphia, W. B. Saunders Co., 1984, p. 231.
3. Leibowitz, H. M., and Kupferman, A.: Therapeutic agents. In Leibowitz, H. M. (ed.): Corneal Disorders. Clinical Diagnosis and Management. Philadelphia, W. B. Saunders Co., 1984, p. 313.
4. Kupferman, A., and Leibowitz, H. M.: Topical

antibiotic therapy of staphylococcal keratitis. Arch. Ophthalmol. 95:1634, 1977.

5. Borrmann, L. R., and Leopold, I. H.: The potential use of quinolones in future ocular antimicrobial therapy. Am. J. Ophthalmol. 106:227, 1988.

6. Judson, P. H.: Aminoglycoside macular toxicity after subconjunctival infection. Case report. Arch. Ophthalmol. 107:1282, 1989.

7. Morris, R. J., McLeod, D., and Gregor, Z. J.: Subconjunctival injection of antibiotics are used increasingly at the conclusion of intraocular and extraocular procedures. Eye 3:860, 1989.

8. Awan, K. J.: Mydriasis and conjunctival paresthesia from local gentamicin. Am. J. Ophthalmol. 99:723, 1985.

9. Sasamoto, K., Akagi, Y., Kodama, Y., and Itoi, M.: Corneal endothelial changes caused by ophthalmic drugs. Cornea 3:37, 1984.

10. Boyle, G. L., Abel, R., Jr., Lazachek, G. W., and Leopold, I. H.: Intraocular penetration of cephalothin. Am. J. Ophthalmol. 74:868, 1972.

11. Brick, D. C., West, C., and Ostler, H. B.: Ocular toxicity of subconjunctival nafcillin. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. St. Louis, C. V. Mosby, 1979, p. 132.

12. Fraunfelder, F.: Drug-Induced Ocular Side Effects and Drug Interactions, ed. 3. Philadelphia, Lea & Febiger, 1989, pp. 13, 30.

13. Baum, J. L.: Antibiotic use in ophthalmology. In Duane, T. D., and Jaeger, E. A. (eds.): Clinical Ophthalmology, vol. 4. Philadelphia, J. B. Lippincott, 1988, p. 6.

14. Osato, M. S., Jensen, H. G., Trousdale, M. D., Bosso, J. A., Borrmann, L. R., Frank, J., and Akers, P.: The comparative in vitro activity of ofloxacin and selected ophthalmic antimicrobial agents against ocular bacterial isolates. Am. J. Ophthalmol. 108:380, 1989.

15. Neu, H.: Microbiologic aspects of fluoroquinolones. Am. J. Ophthalmol. 112(suppl):15S, 1991.

16. O'Brien, T. P., Sawusch, M. R., Dick, J. D., and Gottsch, J. D.: Topical ciprofloxacin of *Pseudomonas* keratitis in rabbits. Arch. Ophthalmol. 106:1444, 1988.

17. Leibowitz, H. M.: Clinical evaluation of ciprofloxacin 0.3% ophthalmic solution for treatment of bacterial keratitis. Am. J. Ophthalmol. 112(suppl):34S, 1991.

Microbiologic Aspects of Fluoroquinolones

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Fluoroquinolones are both old and new antimicrobial agents. The prototype agent of the class, nalidixic acid, was synthesized in 1962, whereas the new fluoroquinolones began to be used in the latter 1980s. During the past six years, orally administered fluoroquinolones have been used extensively in Japan and Europe to treat both community- and hospital-acquired infections. Most recently, one of the fluoroquinolones, ciprofloxacin, has also become available for parenteral and topical ophthalmic use. This article reviews the chemistry, antimicrobial activity, pharmacology, and clinical use of the fluoroquinolones.

THE FLUOROQUINOLONES available for oral use in the United States are structurally related to nalidixic acid (1,8 naphthyridine), first synthesized by Sterling Winthrop Laboratories as an antimalarial agent to treat chloroquine-resistant malaria.[1] Fluoroquinolones differ from nalidixic acid by the presence of the fluorine at position 6 of the molecule (Fig. 1) and by various substitutions at position 7 and position 1. All of the new fluoroquinolones are bicyclic drugs, which contain a carboxyl group at position 3, a keto group at position 4, and a piperazinyl or methyl substituted piperazinyl group at position 7. Differences in the moiety at position 1 markedly alter activity against gram-positive species and *Pseudomonas aeruginosa*. For example, a cyclopropyl group at position 1, as found in the compound ciprofloxacin, yields the optimal in vitro activity against *P. aeruginosa* and some of the enterobacteriaceae. Conversely, a methyl substituted piperazinyl group, as found in lomefloxacin and temafloxacin, markedly increases absorption, prolongs drug half-life, and decreases metabolism. The structures of the fluoroquinolones available and under study in the United States, Japan, and Europe are shown in Figure 2, and the organisms they inhibit are shown in Table 1.

Mechanism of Action

The target of nalidixic acid is the enzyme DNA gyrase, a type 2 topoisomerase composed of four subunits.[2] Topoisomerases are the enzymes responsible for replication, genetic recombination, and DNA repair. DNA gyrase converts negative superhelical coils into covalently closed circular DNA and causes reversible joining of DNA circles, referred to chemically as catenation and decatenation. Quinolones also bind to DNA. There is, in general, fairly good correlation between the inhibition of DNA gyrase activity and the in vitro antimicrobial activity of an agent. Fluoroquinolones kill bacteria as well as inhibit their growth; those organisms not killed initially will not begin to grow again for two to six hours after exposure to a fluoroquinolone. This is called the postantibiotic effect. Since new fluoroquinolones will kill bacteria in the presence of rifampin, tetracycline, and chloramphenicol, protein synthesis is not required for their activity, and fluoroquinolones will kill some resting bacteria (Table 2).

Antimicrobial Activity

The early naphytradine drugs—nalidixic acid, cinoxacin, and oxolinic acid—did not inhibit *P. aeruginosa*, *Staphylococcus aureus*, and organisms such as *Escherichia coli*, *Klebsiella* species, and the like. In contrast, all of the new fluoroquinolones inhibit Enterobacteriaceae at concentrations below 2 μg/ml[3,4] (Table 3). Ciprofloxacin is the most active of the fluoroquinolones. It inhibits 90% of Enterobacteriaceae at concentrations below 0.25 μg/ml, making it two- to eightfold more active than the other

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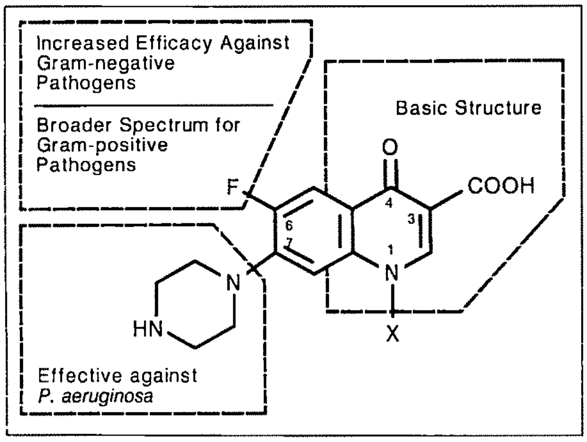

Increased Efficacy Against Gram-negative Pathogens
Broader Spectrum for Gram-positive Pathogens
Basic Structure
O
COOH
F
6
7
4
3
1
N
N
HN
X
Effective against P. aeruginosa

Fig. 1 (Neu). Basic structural modifications of quinolones that contribute to their antibacterial activity. X = a variety of different possible situations. Reprinted with permission from Am. J. Med. 82(suppl 4A):396, 1987.

agents in this class, depending upon the bacterial species. The minimum inhibitory concentration (MIC) of some nalidixic acid resistant organisms tends to be two- to eightfold higher than the MIC against bacteria susceptible to nalidixic acid.

Ciprofloxacin and related agents all inhibit *Haemophilus* species—*H. influenzae, H. parainfluenzae, H. aphrophilus*, and *H. aegyptius*—at extremely low concentrations, less than or equal to 0.06 µg/ml (Table 3). They also inhibit *Neisseria* species such as *N. meningitidis, N. gonorrhoeae, N. sicca*, and *Moraxella* species such as *M.* (*Branhamella*) *catarrhalis* (formerly *N. catarrhalis*) at similarly low concentrations.[3]

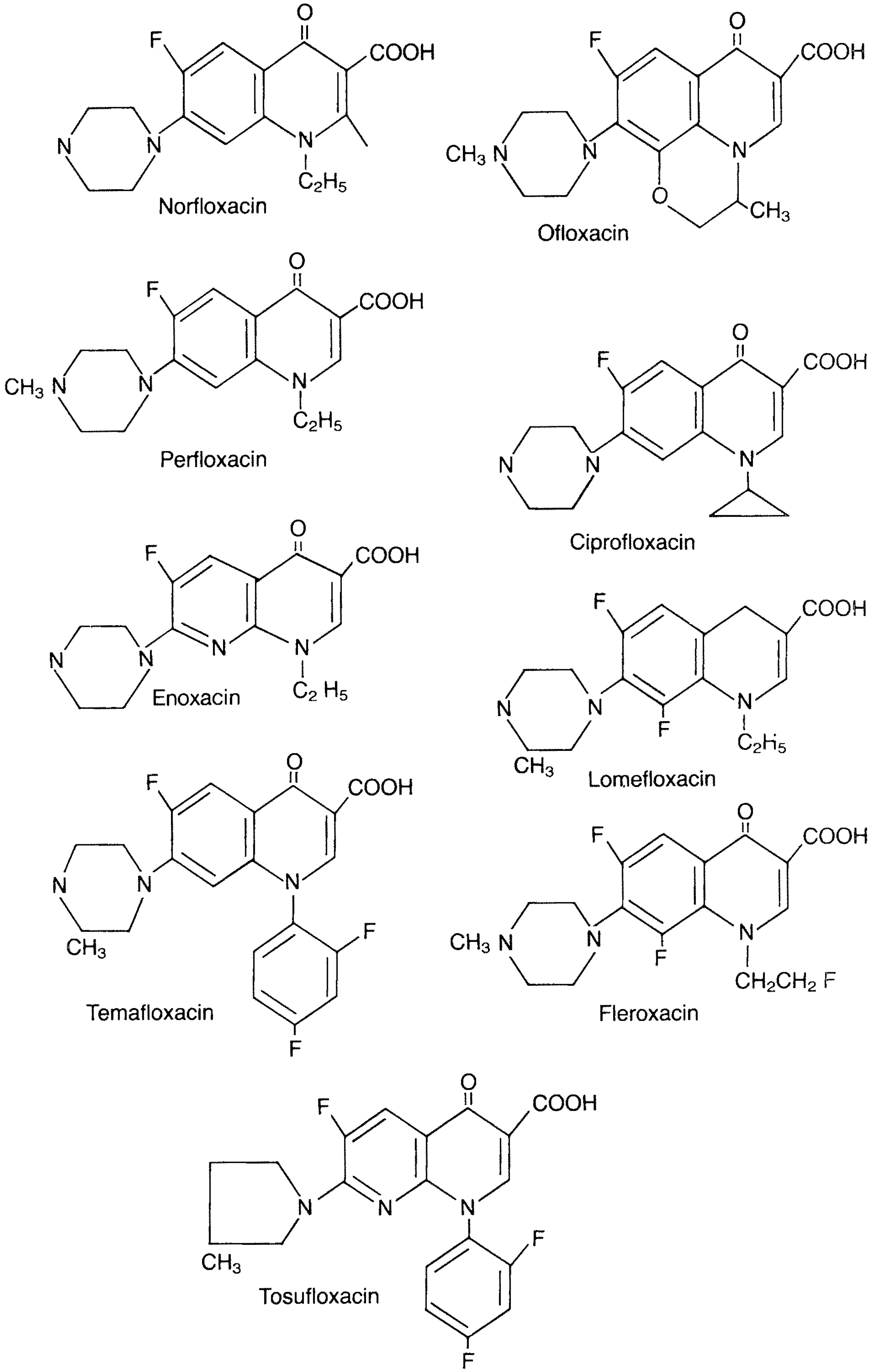
Fluoroquinolones inhibit many intracellular pathogens, such as *Chlamydia trachomatis, C. pneumoniae, Mycoplasma pneumoniae, My. hominis*, and *Legionella pneumoniae*. The activity of fluoroquinolones against organisms such as *Acinetobacter* species, *Xanthomonas maltophilia*, and *Pseudomonas* species other than *P. aeruginosa* is variable, but most organisms are inhibited by 1 to 4 µg/ml.[3,4]

Fluoroquinolones such as ciprofloxacin and ofloxacin inhibit *S. aureus*, including some methicillin-resistant isolates, at an MIC range of 0.5 to 4 µg/ml (Table 3). Agents such as sparfloxacin and tosufloxacin, which are still in clinical investigation, inhibit staphylococci at lower concentrations, 0.12 to 0.25 µg/ml. Most coagulase-negative staphylococci, which include *S. epidermidis, S. haemolyticus, S. capitis, S. simulans*, and *S. saprophyticus*, are inhibited by concentrations of 0.25 to 2 µg/ml. However, the concentrations needed to inhibit *Streptococcus pneumoniae* tend to be higher than those needed to inhibit enterobacteriaceae, with MIC$_{90}$ of 1 to 2 µg/ml for ciprofloxacin and ofloxacin. Agents such as norfloxacin do not adequately inhibit *St. pneumoniae*; MICs are 8 to 16 µg/ml. The same is true of fleroxacin, lomefloxacin and enoxacin. Hemolytic streptococci, such as the group A and B streptococci, *St. pyogenes* and *St. agalactiae*, are inhibited by 1 to 2 µg/ml of ciprofloxacin and ofloxacin, whereas norfloxacin requires concentrations of 8 to 16 µg/ml. *Listeria monocytogenes* and enterococci, *E. faecalis* and *E. faecium*, are inhibited by 2 to 4 µg/ml of ciprofloxacin and ofloxacin but are resistant to norfloxacin.[3]

None of the currently available fluoroquinolones adequately inhibit anaerobic organisms such as *Bacteroides* species and *Clostridium* species but they do inhibit a number of the mouth bacteria such as *Eikenella corrodens* and some fusobacteria, peptostreptococci, and peptococci found in the mouth.[3] Fluoroquinolones do not inhibit any of the fungi that infect the eye such as *Candida* species, *Aspergillus, Fusarium*, and the like.

A number of factors markedly affect the activity of the fluoroquinolones. They are much less active at acid pH 5.5 than at pH 7.4. They are also less active in the presence of some divalent cations such as Al^{2+}, Mg^{2+}, Ca^{2+}, and Fe^{2+}. In contrast to many antimicrobial agents, the number of bacteria and the inoculum size have a minor effect on the activity of the fluoroquinolones. For example, ciprofloxacin kills *E. coli, S. aureus, St. pneumoniae*, and *H. influenzae* whether there are 10^4 colony-forming units or 10^7 colony-forming units. Moreover, the difference between the MIC and the minimal bactericidal concentration is only a single dilution (that is, MIC 0.12 µg/ml and minimal bactericidal concentration 0.25 µg/ml). Minimal bactericidal concentrations of penicillins and cephalosporins often differ by fourfold to 16-fold, particularly for *P. aeruginosa*.

Fluoroquinolones can be combined with other classes of antimicrobial agents without a loss of activity. Thus, they have been used with penicillins, cephalosporins, imipenem, aminoglycosides, clindamycin, erythromycin, and metronidazole when necessary. There is no synergy of fluoroquinolones and aminoglycosides against *P. aeruginosa*, but there is synergy with the ureidopenicillins, azlocillin, and piperacillin against *P. aeruginosa*.



Norfloxacin

Ofloxacin

Perfloxacin

Ciprofloxacin

Enoxacin

Lomefloxacin

Temafloxacin

Fleroxacin

Tosufloxacin

Fig. 2 (Neu). Chemical structures of various quinolones. Reprinted with permission from Infect. Dis. Clin.

Bacterial Resistance

Resistance to nalidixic acid was a major problem; one in 10^6 bacteria became resistant because of a mutation of the DNA gyrase.[5] Fortunately, single-step mutational resistance to ciprofloxacin and related fluoroquinolones occurs at a much lower frequency: 1 in 10^{11} for Enterobacteriaceae, and 1 in 10^9 for *P. aeruginosa* and *S. aureus*. Indeed, the resistance via gyrase actually is trivial for *E. coli* and other organisms (0.06 to 0.25 μg/ml). But for methicillin-resistant *S. aureus* and *P. aeruginosa*, there has been a problem with MIC increasing to levels of 10 to 32 μg/ml, concentrations that are unattainable by the oral route.

In decubitus ulcers, which have a poor blood supply and may not be adequately debrided, patients will develop resistant *S. aureus* (particularly methicillin-resistant *S. aureus*) and *P. aeruginosa*. Resistance in *P. aeruginosa* results from both altered DNA gyrase and alteration of porins (outer membrane proteins) or lipopolysaccharides, which decrease entry of the compounds into the bacterial cell. Similarly, in patients with indwelling catheters that are not changed, development of resistance is a hazard. Nonetheless, the frequency of resistance has been extremely low compared to other antimicrobial classes, with the exception of resistance in *P. aeruginosa*, methicillin-resistant *S. aureus* and *Serratia marcescens*.

It is critical for the ophthalmologist to understand resistance, since the potential for the development of resistance in the eye differs from other infection sites. Use of ciprofloxacin as a topical agent for ophthalmic infections is not a hazard. In a typical case of bacterial keratitis, less than 10^7 organisms infect the cornea. In contrast, an average of 10^9 to 10^{10} infectious organisms are found in chronic wounds and in pulmonary or urinary infections. Depending on the species of bacteria, the frequency of spontaneous resistance to ciprofloxacin is 10^{-9} to 10^{-11}. Furthermore, this form of resistance is related to antibiotic concentration. It generally occurs when the MIC is four to eight times greater than the concentration of antibiotic available at the infection site. Since the MIC of many corneal pathogens is equal to or less than 0.5 μg/ml, a concentration eight times this level is 4 μg/ml. However, ciprofloxacin 0.3% ophthalmic solution contains 3,000 μg/ml of the antibiotic, a concentration that presumably would produce tissue levels greater

TABLE 1
ANTIBACTERIAL SPECTRUM OF FLUORINATED QUINOLONES*

SUSCEPTIBLE† (MIC < 1 μG/ML)	VARIABLE ACTIVITY† (MIC 1 to 2 μG/ML)	INHIBIT† (MIC < 0.5 μG/ML)	RESISTANT SPECIES† (MIC > 4/M/ML)
E. coli	*St. pyogenes*	*Mycoplasma* sp.	*Anaerobic cocci*
K. pneumoniae	Hemolytic streptococci	*Chlamydia* sp.	*Clostridia* sp.
Enterobacter sp.	Groups B, C, F, G	*Legionella* sp.	*Bacteriodes* sp.
Citrobacter sp.	*St. pneumoniae*		
S. marcescens	*St. faecalis*		
Shigella sp.			
Salmonella sp.			
Aeromonas sp.			
Yersinia sp.			
Proteus sp.			
Providencia sp.			
P. aeruginosa			
S. aureus			
S. epidermidis			
Haemophilus sp.			
Neisseria sp.			
Moraxella aeromonas vibrius			
Campylobacter sp.			

*Adapted from Am. J. Med. 82(suppl 4A):397, 1987.

†Including organisms resistant to penicillins, cephalosporins and aminoglycosides.

than eight times the MIC. Repeated topical application of ciprofloxacin 0.3% should prevent resistance.

Pharmacology

All of the fluoroquinolones are absorbed from the gastrointestinal tract.[6,7] Peak serum concentrations usually are achieved one to two hours after the drugs are ingested in the fasting state and approximately two hours when ingested after a meal. However, time to reach peak serum concentrations in elderly individuals and in some patients with markedly depressed renal function may be delayed. Peak serum levels are 1.5 μg/ml after 400 mg of norfloxacin, 4 μg/ml for 400 mg of pefloxacin, 3 μg/ml for 400 mg of enoxacin, 2.5 μg/ml for 500 mg of ciprofloxacin, 4 to 5 μg/ml for 750 mg of ciprofloxacin, and 3.5 to 4 μg/ml for 400 mg of ofloxacin. Serum concentrations above the MIC for enterobacteriaceae are achieved for all of these agents (except norfloxacin) for a period of eight to 12 hours after a dose.

The mean terminal serum half-lives are as follows: ciprofloxacin, three to four hours; norfloxacin, three to four hours; ofloxacin, seven hours; pefloxacin, ten hours; lomefloxacin, eight hours; and fleroxacin, eight hours. In patients with normal renal function, none of the compounds accumulate when administered at usual doses on a 12-hour schedule.

Ciprofloxacin and ofloxacin have been used by the intravenous route. In general, a serum concentration of 1 μg/ml is achieved for each 100 mg infused intravenously.

The quinolones are widely distributed in body tissues and fluids, and enter phagocytic cells. Studies of chemically or mechanically induced blister fluid, which represents interstitial fluid, indicate that concentrations ranging from 50% to 80% of peak serum concentrations are achieved in the first several hours after a dose, and concentrations in interstitial fluid exceed serum concentrations later. The quinolones have extremely large apparent volumes of distribution, ranging from 80 to 150 liters compared with volumes of distribution of 25 liters for beta-lactams and aminoglycosides. For agents such as ciprofloxacin and ofloxacin, the lung, liver, heart, bone, and prostate concentrations exceed the inhibitory levels for most enterobacteriaceae, staphylococci, *Haemophilus*, and *Neisseria* species. The concentrations for hemolytic streptococci and *S. pneumoniae* are inadequate for some agents. Quinolones achieve high concentrations in salivary and lacrimal secretions, nasal mucosa, and bronchial epithelium. The quinolones such as ciprofloxacin, norfloxacin, and ofloxacin enter polymorphonuclear leukocytes and alveolar macrophages, producing concentrations of 3 to 8 μg/ml. Concentrations in the cerebral spinal fluid are low even in the presence of inflammation. The highest concentrations have been reported for pefloxacin at 4 μg/ml, followed by ofloxacin. Following topical instillation, ciprofloxacin penetrates through the cornea into the aqueous humor.[8,9]

Quinolones differ in the manner they are removed from the body. Renal mechanisms are most important for ofloxacin, fleroxacin, temafloxacin, and lomefloxacin, hepatic mechanisms for pefloxacin. Both renal and hepatic mechanisms are utilized by ciprofloxacin, norfloxacin, and enoxacin. Quinolones can undergo metabolism in the liver by glucuronidation, hydroxylation, and oxidation, depending on the partic-

TABLE 2
IMPORTANT MICROBIOLOGIC ASPECTS OF QUINOLONE ANTIMICROBIAL AGENTS*

- Close relation of MIC and minimal bactericidal concentrations with minor inoculum effect for most organisms
- Prolonged postantibiotic effect on staphylococci, enterobacteriaceae, and *Pseudomonas* sp.
- Do not select resistant mutants of plasmid type
- Do not kill protective intestinal streptococcal and anaerobic species
- Frequency of mutational resistance is low (less than 10^{-11} to 10^{-9})
- Inhibit aminoglycoside- and beta-lactam-resistant bacteria
- Can be used with other antimicrobial agents

*Adapted from Am. J. Med. 82(suppl 4A):397, 1987.

ular compound. All of the quinolones are renally excreted, varying from a low 11% for pefloxacin to 90% plus for ofloxacin. Renal excretion is by tubular secretion and glomerular filtration. Peak urine concentrations of quinolones exceed the minimal bactericidal concentrations of most urinary pathogens. Concentrations in urine in excess of 10 μg/ml can be detected up to 24 hours after ingestion of a dose of the longer-acting agents. Reduced renal function prolongs the half-life of ciprofloxacin and norfloxacin by a moderate degree; only in the presence of anuria does the half-life double to the range of approximately ten hours. Fluoroquinolones are also excreted in the large intestine.

In the eye ciprofloxacin is applied as a topical solution of 0.3%. This is 3 g/100 ml or 3 mg/ml or 3,000 μg/ml, far above the MIC of virtually all eye pathogens except fungi and viruses. At this concentration there is minimal ocular irritation, and there is diffusion into the cornea and other ocular tissues at levels well in excess of the MIC of the usual corneal and conjunctival pathogens, such as *S. aureus*, coagulase-negative staphylococci, *Neisseria, Moraxella, Haemophilus* species, Enterobacteriaceae, and *P. aeruginosa*.[8,9]

Clinical Use Of Fluoroquinolones

Urinary Tract Infections

All of the new quinolones have activity against the major urinary pathogens such as the Enterobacteriaceae and *P. aeruginosa*, including many microorganisms resistant to aminoglycosides, beta-lactams, and trimethoprim. Quinolones have been effective in the treatment of uncomplicated cystitis, and they reduce the frequency of urinary tract infections in women.[10] Given their pharmacology and effect on vaginal flora, three days of treatment is as effective as treatment for seven to ten days.

Quinolones are useful for complicated urinary tract infections, particularly as replacement for parenteral antibiotics, significantly reducing the need for hospitalization and treatment costs.[11] They are also useful in hospital-acquired urinary infections, since they eliminate enterobacteriaceae and *Pseudomonas* species from fecal contents and prevent rapid reinfection.[12] However, resistance occurs in patients in whom indwelling urethral catheters have been left in place.

Ciprofloxacin, ofloxacin, and lomefloxacin have proven successful in eradicating *E. coli* in cases of prostatitis.[13] However, in most studies, patients with infection caused by *P. aeruginosa* and enterococci have had relapses.

Sexually Transmitted Diseases

Fluoroquinolones have proven effective for the treatment of gonococcal urethritis and also may be useful in the therapy of pharyngeal and rectal infection.[10] Their use in the treatment of *Chlamydia* species infections is less satisfactory. Norfloxacin is not adequate therapy for chlamydial infections.[14] Ciprofloxacin at a twice-daily dose of 750 mg or 1,000 mg has been less effective than doxycycline at 100 mg twice daily. Ofloxacin, on the other hand, at doses of 400 mg twice a day for seven days appears to be as effective as doxycycline for eradicating *Chlamydia* species in both males and females. Chancroid caused by *H. ducreyii* has been cured by single doses of ciprofloxacin, norfloxacin, enoxacin, ofloxacin, and fleroxacin.[15] Recurrences are common in patients with human immunodeficiency virus infection. None of the quinolones are appropriate therapy for syphilis.

Upper Respiratory Tract Infections

Quinolones are not the first choice of therapy for pharyngitis, sinusitis, or otitis media. The one upper respiratory infection for which a quinolone would be appropriate is necrotizing external otitis caused by *P. aeruginosa*, which occurs in diabetic patients; oral treatment with ciprofloxacin results in clinical cures comparable to those achieved with parenteral agents.[16,17]

Lower Respiratory Tract Infections

There have been extensive studies of quinolones in lower respiratory tract infections.[18] Orally administered ciprofloxacin has been evaluated in the United States, Europe, and Japan. The majority of patients have had bronchitis, and in these studies ciprofloxacin was equivalent to ampicillin, amoxicillin, doxycycline, trimethoprim/sulfamethoxazole, and superior to oral cephalosporins such as cephalexin. Serious gram-negative nosocomial respiratory infections have been treated with ciprofloxacin with results comparable to those achieved with parenteral penicillins and cephalosporins.[19] Pneumococcal bacteremia has occurred in patients receiving ciprofloxacin, so it should not be a first choice.[20]

TABLE 3

COMPARATIVE IN VITRO ACTIVITY OF QUINOLONE ANTIBIOTICS*

	CIPROFLOXACIN	NORFLOXACIN	OFLOXACIN	ENOXACIN	LOMEFLOXACIN	FLEROXACIN	TEMAFLOXACIN	TOSUFLOXACIN
ORGANISM	MIC$_{90}$ (μG/ML)							
E. coli	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.12
K. pneumoniae	0.12	0.5	0.25	0.25	0.5	0.5	0.5	0.06
Enterobacter sp.	0.12	1	0.25	0.5	0.5	0.5	0.25	0.25
Citrobacter sp.	0.12	1	0.25	0.25	1	0.5	2	0.12
Se. marcescens	0.25	2	2	2	2	2	4	0.25
Shigella sp.	0.12	0.25	0.25	0.25	0.25	0.25	0.5	0.12
Proteus mirabilis	0.12	0.25	0.25	0.25	0.25	0.25	0.5	0.12
Other sp.	0.25	0.5	0.5	0.5	1	0.5	1	0.12
Morganella morganii	0.12	0.5	0.12	2	0.5	0.5	1	0.25
Providencia sp.	0.25	2	0.5	2	0.25	0.25	1	0.12
Yersinia enterocolitica	0.12	0.25	0.12	0.25	4	4	4	0.25
P. aeruginosa	0.5	8	4	2	0.5	0.5	0.25	0.12
Acinetobacter sp.	1	8	1	8	4	4	4	0.5
S. aureus methicillin-susceptible	0.5	1	0.5	2	4	2	1	0.12
S. aureus methicillin-resistant	0.5	4	0.5	4	2	2	0.5	0.12
S. epidermidis	0.5	2	2	8	2	2	0.5	0.25
Enterococci sp.	2	8	4	6	1	2	0.5	0.5
Streptococcus sp. (Group A)	1	4	2	8	16	8	2	0.12
Streptococcus sp. (Group B)	1	8	2	16	8	8	0.5	0.25
St. pneumoniae	2	8	2	16	16	16	1	0.25
H. influenzae	<0.06	<0.12	<0.12	<0.12	8	8	0.25	<0.12
N. gonorrhoeae	<0.06	<0.12	<0.12	<0.12	0.12	0.12	0.12	<0.12
N. meningitidis	<0.06	<0.12	<0.12	<0.12	0.12	0.12	0.12	<0.12
Campylobacter sp.	0.05	0.05	1	1	0.12	0.12	0.12	<0.12
Bacteroides fragilis	16	>32	8	>32	—	—	4	1
B. melaninogenicus	8	>32	8	>32	64	—	4	2
Peptostreptococcus sp.	4	>32	2	>32	16	—	4	2
Mycobacterium tuberculosis	1	—	1	—	16	—	—	—
Branhamella catarrhalis	<0.12	<0.12	<0.12	<0.12	—	—	<0.12	<0.12
Brucella sp.	1	8	2	8	0.12	—	—	—
Listeria monocytogenes	2	4	2	8	—	—	0.25	0.25
Corynebacterium JK	1	4	1	8	8	—	0.25	0.25
Legionella sp.	<0.12	0.5	<0.25	0.5	—	—	0.25	0.25
C. trachomatis	2	8	1	8	0.25	—	0.12	0.25
Mycoplasma hominis	0.5	32	1	64	1	—	—	0.5
Ureaplasma sp.	2	32	2	64	—	—	—	—
M. pneumoniae	1	8	1	8	—	—	—	—

*Median MIC$_{90}$ of the new quinolone antibiotics was 1 μg/mL. Based on published results from multiple studies. Reprinted with permission from Infect. Dis. Clin. 3:628, 1989.

Cystic Fibrosis

Patients have serious infections caused by *P. aeruginosa* against which orally administered ciprofloxacin and ofloxacin have been effective.[21,22] However, resistance has developed so therapy should not be prolonged or repeated too frequently. Quinolones do not have a role in aspiration pneumonia caused by the anaerobic and microaerophilic mouth flora.

Diarrheal Diseases

All of the quinolones have been effective in the treatment of bacterial pathogens causing diarrhea.[23,24] In general, within 48 hours, pathogenic bacteria are eradicated from the intestine, although *Campylobacter* may persist for a slightly longer period of time. Resistance has not been a major problem. Ciprofloxacin, norfloxacin, or ofloxacin are effective therapy of *Salmonella typhi*, particularly strains resistant to trimethoprim. Quinolones are not used in pediatrics where diarrhea is the most life-threatening event. For a traveler, 500 mg of ciprofloxacin orally will stop diarrhea caused by toxigenic *E. coli* and other pathogens 12 hours after a single 500-mg dose.

Osteomyelitis and Septic Arthritis

Quinolones represent a significant advance in the therapy of osteomyelitis. They inhibit many of the resistant gram-negative organisms seen in infections of soft tissue near osteomyelitis that follows trauma or surgery.[25,26] Ciprofloxacin and ofloxacin have been the most widely used agents to date. The failure rate is approximately 15%. *Pseudomonas* has been the organism that is most often treated. Patients with both methicillin-susceptible and methicillin-resistant *S. aureus* have been treated, with results comparable to those achieved against aerobic gram-negative species. Resistance has been noted to develop with *P. aeruginosa*, methicillin-resistant *S. aureus*, *Serratia* species, and *Enterobacter* species. Patients have been able to tolerate therapy for up to six months or longer.

Skin Infections

There have been extensive studies of ciprofloxacin and ofloxacin as therapy of mixed aerobic, gram-negative and gram-positive skin infections occurring in hospitalized patients.[27,28] Ciprofloxacin and ofloxacin are equivalent to parenteral therapy of such infections. Since there is little activity against anaerobic species, it is necessary to use an agent with anaerobic activity in combination with the quinolone.

Other Infections

Ciprofloxacin combined with rifampin has proven to be effective therapy of staphylococcal endocarditis in narcotic addicts.[29] Ciprofloxacin and pefloxacin have been used to treat some patients with meningitis, but their precise role is not established.

Ocular Infections

The results of therapy with ciprofloxacin as an agent to treat conjunctivitis and corneal ulcers caused by bacteria are impressive and detailed elsewhere in this issue. In our own unpublished studies, ciprofloxacin was more effective than vancomycin in treatment of methicillin-resistant *S. aureus* corneal ulcers in rabbits. In view of this, we would regard ciprofloxacin as a major advance in the treatment of ocular infections.

Adverse Reactions

Adverse reactions have been reported with the use of all antimicrobial agents. However, the overall frequency of clinically adverse experiences encountered with ciprofloxacin, norfloxacin, ofloxacin, and the fluoroquinolone agents still under investigation have been relatively low.[30,31] A small percentage (less that 2.5%) of patients treated with norfloxacin, ciprofloxacin, and ofloxacin have had adverse reactions severe enough to require cessation of treatment. In general, gastrointestinal symptoms have been the most frequently reported side effects of these drugs, occurring in 3% to 5% of patients overall. The symptoms have included nausea, vomiting, abdominal discomfort, and anorexia. Diarrhea has been particularly infrequent and development of antibiotic-associated colitis as detected by *Clostridium difficile* cytotoxin has been rare.

Central nervous system reactions caused by the fluoroquinolones occur in 1% to 4% of patients. The most common symptom has been mild headache or slight dizziness, followed by sleep disturbance or some alteration of mood such as agitation, anxiety, or depression. Seizures rarely have been reported, primarily in patients who are simultaneously receiving theophylline and enoxacin or ciprofloxacin. Certain noncorticosteroidal anti-inflammatory agents used with enoxacin also may predispose to seizures.

Dermatologic reactions to fluoroquinolones, although infrequent, occur in up to 2% of patients. The most common has been nonspecific rash. Photosensitivity after excess light exposure occurs, but the skin rashes have cleared rapidly. Fulminant skin reactions are rare.

In juvenile animals, quinolones produce cartilage erosion in weight-bearing joints and inhibit limb bud growth; therefore, fluoroquinolones are not used in children.

Hematologic abnormalities are infrequent in patients receiving fluoroquinolones. Mild leukopenia has been reported in a small number of patients as has been mild anemia. Liver function tests and serious hepatic disease are rare. Interstitial nephritis and hematuria have been rarely reported.

Ocular toxicities have not been seen in humans receiving these newer fluoroquinolones systemically.

Drug-Drug Interactions

There have been few drug-drug interactions involving fluoroquinolones.[32] Enoxacin will cause accumulation of theophylline, as will ciprofloxacin to a lesser extent. Caffeine elimination is prolonged by the administration of most quinolones. Antacids containing magnesium or aluminum and even high doses of calcium or iron preparations will markedly impair the absorption of orally administered fluoroquinolones. Thus, a fluoroquinolone should not be ingested within four hours of taking antacids orally.

The quinolone antimicrobial agents are major therapeutic compounds. They are particularly useful in treatment of serious urinary tract, diarrheal, bone and joint, and selected respiratory tract infections. Improper use of these agents will lead to resistance, but this should not be a problem for use in the eye. Adverse reactions have been infrequent. Appropriate use of these agents will ensure their continued value in systemic and ophthalmic infections during the coming decade.

References

1. Lesher, G. Y., Froelich, E. D., Gruet, M. D., Bailey, J. H., and Brundage, R. P.: 1,8-Naphthyridine derivatives. A new class of chemotherapeutic agents. J. Med. Pharm. Chem. 5:1063, 1962.
2. Gellert, M., Mizuuchi, K., O'Dea, M. H., Itoh, T., and Tomizawa, J. I.: Nalidixic acid resistance. A second genetic character involved in DNA gyrase activity. Proc. Natl. Acad. Sci. USA 74:4772, 1977.
3. Neu, H. C.: The quinolones. Infect. Dis. Clin. North Am. 3:625, 1989.
4. Eliopoulos, G. M., and Eliopoulos, C. T.: Quinolone antimicrobial agents activity in vitro. In Wolfson, J. S., and Hooper, D. C. (eds.): Quinolone Antimicrobial Agents, vol. 3. Washington, D.C., American Society for Microbiology, 1989, pp. 35–70.
5. Neu, H. C.: Bacterial resistance to fluoroquinolones. Rev. Infect. Dis. 10(suppl 1):57, 1988.
6. Wise, R., Lister, D., McNulty, C. A. M., Griggs, D., and Andrews, J. M.: The comparative pharmacokinetics of five quinolones. J. Antimicrob. Chemother. 18(suppl D):71, 1986.
7. Bergan, T.: Pharmacokinetics of fluorinated quinolones. In Andriole, V. T. (ed.): The Quinolones, vol. 4. London, Academic Press, 1988, pp. 119–154.
8. O'Brien, T. P., Sawusch, M. R., Dick, J. D., and Gottsch, J. D.: Topical ciprofloxacin treatment of *Pseudomonas* keratitis in rabbits. Arch. Ophthalmol. 106:1444, 1988.
9. Reidy, J. J., Hobden, J. A., Hill, J. M., Forman, K., and O'Callaghan, R. J.: The efficacy of topical ciprofloxacin and norfloxacin in the treatment of experimental *Pseudomonas* keratitis. Cornea 10:25, 1991.
10. Naber, K. G.: Use of quinolones in urinary tract infections and prostatitis. Rev. Infect. Dis. 11(suppl 5):1372, 1989.
11. Malinverni, R., and Glaser, M. P.: Comparative studies of fluoroquinolones in the treatment of urinary tract infections. Rev. Infect. Dis. 10(suppl 1):153, 1988.
12. Wolfson, J.S., and Hooper, D.C.: Treatment of genitourinary tract infections with fluoroquinolones. Activity in vitro, pharmacokinetics, and clinical efficacy in urinary tract infections and prostatitis. Antimicrob. Agents. Chemother. 33:1655, 1989.
13. Weidner, W., Schiefer, H. G., and Dalhoff, A.: Treatment of chronic bacterial prostatitis with ciprofloxacin. Results of a one-year follow-up study. Am. J. Med. 82(suppl 4A):280, 1987.
14. Bowie, W. R., Willetts, V., and Sibau, L.: Failure of norfloxacin to eradicate *Chlamydia trachomatis* in nongonococcal urethritis. Antimicrob. Agents Chemother. 30:594, 1986.
15. Naamara, W., Plummer, F. A., Greenblatt, R. M., D'Costa, L. J., Ndinya-Achola, J. O., and Ronald, A. R.: Treatment of chancroid with ciprofloxacin. A prospective, randomized clinical trial. Am. J. Med. 82(suppl 4A):317, 1987.
16. Lang, R., Goshen, S., Kitzes-Cohen, R., and Sade, J.: Successful treatment of malignant external otitis with oral ciprofloxacin. Report of experience with 23 patients. J. Infect. Dis. 161:537, 1990.
17. Rubin, J., Stoehr, G., Yu, V. L., Muder, R. R., Matador, A., and Kamerer, D. B.: Efficacy of oral ciprofloxacin plus rifampin for treatment of malignant external otitis. Arch. Otolaryngol. Head Neck Surg. 115:1063, 1989.
18. Chodosh, S., Tuck, J., Stottmeier, K. D., and Pizzuto, D.: Comparison of ciprofloxacin with ampicillin in acute infectious exacerbations of chronic bronchitis. A double-blind crossover study. Am. J. Med. 87(suppl 5A):107S, 1989.
19. Khan, F. A., and Basir, R.: Sequential intravenous-oral administration of ciprofloxacin vs. ceftazi-

dime in serious bacterial respiratory tract infections. Chest 96:528, 1989.

20. Cooper, B., and Lawlor, M.: Pneumococcal bacteremia during ciprofloxacin therapy for pneumococcal pneumonia. Am. J. Med. 87:475, 1989.

21. Hodson, M. E., Roberts, C. M., Butland, R. J. A., Smith, M. J., and Batten, J. C.: Oral ciprofloxacin compared with conventional intravenous treatment for *Pseudomonas aeruginosa* infections in adults and cystic fibrosis. Lancet 1:235, 1987.

22. Jensen, T., Pedersen, S. S., Hoiby, N., and Koch, C.: Efficacy of oral fluoroquinolones vs. conventional intravenous antipseudomonal chemotherapy in treatment of cystic fibrosis. Eur. J. Clin. Microbiol. 6:618, 1987.

23. DuPont, H. L.: Quinolone antimicrobial agents in the management of bacterial enteric infections. In Wolfson, J. S., and Hooper, D. C. (eds.): Quinolone Antimicrobial Agents. Washington, D.C., American Society for Microbiology, 1989, pp. 167–176.

24. Murray, B. E.: Quinolones and the gastrointestinal tract. Eur. J. Clin. Microbiol. Infect. Dis. 8:1093, 1989.

25. Gentry, L. O., and Rodriguez, G. G.: Oral ciprofloxacin compared with parenteral antibiotics in the treatment of osteomyelitis. Antimicrob. Agents Chemother. 34:40, 1990.

26. Hoogkam-Korstanje, J. A., von Bottenburg, H. A., van Bruggen, J., Davidson, J. S. A., Detmar, S. J., de Graf, W., Rijnks, J., Ypma, J. F. A. M., and de Zwart, D. F.: Treatment of chronic osteomyelitis with ciprofloxacin. J. Antimicrob. Chemother. 23:427, 1989.

27. Gentry, L. O., and Koshdel, A.: Intravenous/oral ciprofloxacin versus intravenous ceftazidime in the treatment of serious gram-negative infections of the skin and skin structure. Am. J. Med. 87(suppl 5A):132S, 1989.

28. Fass, R. J.: Treatment of skin and soft tissue infections with oral ciprofloxacin. J. Antimicrob. Chemother. 18(suppl D):153, 1986.

29. Dworkin, R. J., Lee, B. L., Sande, M. A., and Chambers, H. F.: Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug users with ciprofloxacin and rifampicin. Lancet 2:1071, 1989.

30. Halkin, H.: Adverse effects of the fluoroquinolones. Rev. Infect. Dis. 10(suppl 1):S258, 1988.

31. Christ, W., Lehnert, T., and Ulbrich, B.: Specific toxicologic aspects of the quinolones. Rev. Infect. Dis. 10(suppl 1):S141, 1988.

32. Davies, B. I., and Maesen, F. P.: Drug interactions with quinolones. Rev. Infect. Dis. 11(suppl 5):S1083, 1989.

Insights From Experimental Data On Ciprofloxacin in the Treatment of Bacterial Keratitis and Ocular Infections

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Ciprofloxacin is a potent fluoroquinolone antibiotic with in vitro activity against many significant gram-positive and gram-negative ocular pathogens. A review of the experimental studies of this antibiotic shows bactericidal activity, a broad antimicrobial spectrum, and a low incidence of resistance. The growing body of experimental data supports the effectiveness of ciprofloxacin in the treatment of experimental keratitis and suggest that it be evaluated further in ocular infections.

EARLY INITIATION OF effective antimicrobial chemotherapy is key to the successful management of bacterial keratitis. Because of the potential for rapid tissue destruction and loss of vision, administration of potent, broad-spectrum antibiotics must be started before culture and sensitivity data are available. Unfortunately, clinicians are faced with an increasing number of resistant strains of bacterial pathogens.

Ciprofloxacin, a member of the fluoroquinolone family of antibiotics, has been investigated for topical use in ocular infections because of its broad spectrum of antibacterial activity. Derived from the basic structure of nalidixic acid, structural modifications and substitutions have yielded a bactericidal drug with in vitro activity against most of the significant gram-positive and gram-negative ocular pathogens.[1-6] Like the other quinolone antibiotics, ciprofloxacin inhibits bacterial DNA gyrase, an enzyme responsible for supercoiling and sealing of nicked DNA strands and therefore essential for bacterial replication. The resultant damage to the bacterial chromosome leads to bacterial cell death. Its broad spectrum of activity, coupled with an extremely low incidence of resistance,[1,2,5] prompted investigation of ciprofloxacin as a topical agent for use in ophthalmic infections.

A knowledge of likely etiologic agents is crucial for appropriate antibiotic selection. Common bacterial isolates from ulcerative keratitis include *Staphylococcus aureus, S. epidermidis, Streptococcus pneumoniae, Pseudomonas aeruginosa,* and other gram-negative rods.[7-9] Their incidence varies depending on geographic locale.[7] Broad-spectrum coverage that includes these pathogens is a requisite for the initial antibiotics chosen to treat a bacterial corneal ulcer in order not to delay effective therapy while awaiting culture and sensitivity results.

In Vitro Bacterial Sensitivity

Ciprofloxacin has in vitro activity against all of the aforementioned ocular pathogens.[1-6] In their extensive review, Campoli-Richards and associates[3] reported the susceptibility of all species of enterobacteriaceae (except for some species of *Providencia*) to ciprofloxacin with minimum inhibitory concentration (MIC_{90}) values of less than or equal to 1 μg/ml. *Pseudomonas aeruginosa* was susceptible to ciprofloxacin with an MIC_{90} range of 0.12 to 1.0 μg/ml.

Ciprofloxacin is active against gram-positive organisms as well. *Staphylococcus* species, including beta lactamase-producing and methicillin-resistant strains of *S. aureus*, had MIC_{90} values of 0.12 to 1.0 μg/ml. Although less active against the streptococci, MIC_{90} values were still between 1.0 and 4.0 μg/ml. Other ocular pathogens susceptible to ciprofloxacin included *Neisseria, Haemophilus,*[3] and *Chlamydia trachomatis.*[10] Thus, ciprofloxacin has in vitro activity against most of the bacterial pathogens

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important in external ocular infections (Table). Moreover, the minimal bactericidal concentration of ciprofloxacin against significant ocular pathogens is between one to two times the MIC for most isolates.[11]

Penetration Data

O'Brien and associates[12] showed that after topical application, therapeutic concentrations of ciprofloxacin were achieved in the aqueous humor of rabbits when the corneal epithelium was intact as well as after it had been debrided. In the presence of an intact epithelium, instillation of six doses of ciprofloxacin 0.3% at 30-minute intervals yielded an aqueous humor concentration of the drug of 4.82 ± 2.15 μg/ml 30 minutes after the last dose had been administered. After debridement of the corneal epithelium, a threefold increase in aqueous concentration was demonstrated (12.9 ± 4.39 μg/ml). These aqueous humor levels substantially exceed the reported MIC for important corneal pathogens.

Reidy and associates[13] studied the aqueous humor concentrations of ciprofloxacin 0.75% vs norfloxacin 1%. Following topical administration of drops every 15 minutes for four doses, then every 30 minutes for six doses, these investigators found higher aqueous humor concentrations of ciprofloxacin (30.5 μg/ml) than norfloxacin (7.5 μg/ml). They concluded that this accounted for the greater reduction in bacterial colony forming units by ciprofloxacin (in comparison to norfloxacin) documented by their study.

TABLE
IN VITRO ACTIVITY OF CIPROFLOXACIN AGAINST COMMON OCULAR PATHOGENS

BACTERIA	MIC_{90} (μG/ML)
Staphylococcus aureus	0.61
S. epidermidis	0.49
Streptococcus pneumoniae	1.97
Haemophilus influenzae	0.03
Pseudomonas aeruginosa	0.73
Proteus mirabilis	0.18
Klebsiella pneumoniae	0.24
Escherichia coli	0.08
Neisseria gonorrhoeae	0.09
Morganella morganii	0.13
Chlamydia trachomatis	0.5–1

Therapeutic Effectiveness

Pseudomonas aeruginosa is one of the most commonly encountered bacterial pathogens, especially in cases of contact lens-associated bacterial keratitis.[14-16] Resistant strains are becoming more prevalent, accounting for as high as 8% to 10% of *Pseudomonas* keratitis.[17-19] This organism can produce a rapidly progressive, necrotizing keratitis, making prompt institution of effective antibiotic therapy crucial.

A number of investigators have studied the antibacterial effectiveness of ciprofloxacin in experimental keratitis. O'Brien and associates[12] demonstrated in vivo efficacy in rabbits of topical ciprofloxacin in treatment of experimental keratitis caused by an aminoglycoside-resistant strain of *P. aeruginosa*.[12] Treatment was begun five hours after intrastromal inoculation of the organism and was continued at 30-minute intervals for 12 hours. The corneas were then excised and processed for enumeration of bacterial colony-forming units. Untreated controls had colony-forming units of 3.1 × 10^7 organisms per milliliter of corneal specimen recovered. Bacterial colony-forming units for ciprofloxacin-treated corneas were zero.

Reidy and associates[13] compared the efficacy of ciprofloxacin 0.75%, norfloxacin 1%, and tobramycin 1.36% in the treatment of experimental *Pseudomonas* keratitis. The aminoglycoside-resistant *P. aeruginosa* strain studied had MIC values of 31.25 μg/ml for tobramycin, 0.48 μg/ml for norfloxacin, and 0.24 μg/ml for ciprofloxacin. In comparison to untreated controls, they found a reduction of five log units in the number of bacterial colony-forming units in corneas treated with ciprofloxacin and a reduction of two log units in corneas treated with norfloxacin. Both values were highly significant statistically. As expected, both fluoroquinolone antibiotics were significantly more effective than fortified tobramycin in this experimental model.

Another factor in evaluating therapeutic efficacy is postantibiotic effect. This is a measure of the continued suppression of bacterial growth after limited exposure to an antibiotic. Chin and Neu[20] demonstrated a significant postantibiotic effect for ciprofloxacin against many gram-negative organisms, including *P. aeruginosa*, and against *S. aureus*, with a recovery range of one to six hours. The clinical significance of a postantibiotic effect in the treatment of external ocular infections is not known. We believe it has theoretic importance because peak antibiotic levels are not maintained with intermittent instillation of antibiotic to the cornea and subsequent run-off into the lacrimal drainage system. Therefore, any postantibiotic effect would allow for persistent inhibition of bacterial cell replication during a trough interval before the next dose of antibiotic is applied. Further study of ciprofloxacin levels in the preocular tear film and its relationship to corneal stromal and aqueous levels is needed.

Resistance Data

With ciprofloxacin's extended spectrum and potential for widespread use, concern arises about potential emergence of resistant organisms. Data thus far indicate an exceedingly low incidence of resistance. Plasmid-mediated resistance does not occur.[21,22] Thus, a chromosomal mutation is required if an organism is to develop resistance to ciprofloxacin. Spontaneous mutational frequencies are low, ranging from 10^{-7} to 10^{-9}.[1,2,5] Indeed, some investigators believe that resistance may require more than one chromosomal mutation.[23]

Bacteria resistant to beta-lactam antibiotics and methicillin-resistant *S. aureus* are susceptible to ciprofloxacin.[3] Except for strains of *Providencia stuartii* resistant to both aminoglycosides and ciprofloxacin, organisms that produce aminoglycoside-neutralizing enzymes are generally susceptible to ciprofloxacin. No linked resistance appears to exist between the 4-quinolones, beta-lactams, and aminoglycosides.[6] Moreover, when Smith[22] studied resistant strains of *Escherichia coli*, he found that mutational resistance was relative; MICs were still low (0.22 to 0.5 μg/ml). True therapeutic resistance did not occur among resistant mutants of *E. coli*.

Ciprofloxacin holds promise as an effective new agent for treating bacterial keratitis. Its broad antimicrobial spectrum and low incidence of resistance may allow for single-agent therapy in the initial management of bacterial keratitis, a positive factor in patient compliance. This agent shows excellent bactericidal activity against *Pseudomonas* as well as against most other important corneal pathogens. Ocular penetration data demonstrate adequate bioavailability after topical administration; aqueous humor concentrations exceed the MIC for most organisms. A postantibiotic effect may potentiate its therapeutic efficacy.

Conventional therapy of bacterial keratitis calls for the use of fortified topical preparations of an aminoglycoside and a cephalosporin. The problems associated with the use of fortified topical antibiotics are well known but unavoidable in the absence of an acceptable alternative. These problems may be reduced by the availability of a commercially formulated ophthalmic solution of ciprofloxacin 0.3%.

Ciprofloxacin's antimicrobial spectrum also suggests excellent coverage in the treatment of bacterial conjunctivitis. Other future applications of ciprofloxacin might include perioperative prophylaxis, intravitreal injection for bacterial endophthalmitis, and systemic administration for both ocular and periocular infections. The therapeutic and safety advantages of topical ophthalmic ciprofloxacin warrant its evaluation in a variety of ophthalmic infections.

References

1. Chin, N.-X., and Neu, H. C.: Ciprofloxacin, a quinolone carboxylic acid compound active against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. 25:319, 1984.
2. Wolfson, J. S., and Hooper, D. C.: The fluoroquinolones. Structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob. Agents Chemother. 28:581, 1985.
3. Campoli-Richards, D. M., Monk, J. P., Price, A., Benfield, P., Todd, P. A., and Ward, A.: Ciprofloxacin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 35:373, 1988.
4. Barza, M.: Pharmacokinetics and efficacy of the new quinolones in infections of the eye, ear, nose, and throat. Rev. Infect. Dis. 10(suppl 1):241, 1988.
5. Sanders, C. C., Sanders, W. E., and Goering, R. V.: Overview of preclinical studies with ciprofloxacin. Am. J. Med. 82(suppl 4A):2, 1987.
6. King, A., and Phillips, I.: The comparative in vitro activity of eight newer quinolones and nalidixic acid. J. Antimicrob. Chemother. 18(suppl D):1, 1986.
7. Hyndiuk, R. A., and Snyder, R. W.: Bacterial keratitis. In Smolin, G., and Thoft, R. A. (eds.): The Cornea, Scientific Foundations and Clinical Practice. Boston, Little, Brown and Company, 1987, pp. 193–194.
8. Asbell, P., and Stenson, S.: Ulcerative keratitis, survey of 30 years' laboratory experience. Arch. Ophthalmol. 100:77, 1982.

9. Hyndiuk, R. A., Skorich, D. N., and Burd, E. M.: Bacterial keratitis. In Tabbara, K. F., and Hyndiuk, R. A. (eds.): Infections of the Eye. Boston, Little, Brown and Company, 1986, pp. 309–311.

10. Heessen, F. W. A., and Muytjens, H. L.: In vitro activities of ciprofloxacin, norfloxacin, pepemidic acid, cinoxacin, and nalidixic acid against chlamydia trachomatis. Antimicrob. Agents Chemother. 25:123, 1984.

11. Reeves, D. S., Bywater, M. J., Holt, H. A., and White, L. O.: In vitro studies with ciprofloxacin, a new 4-quinolone compound. J. Antimicrob. Chemother. 13:333, 1984.

12. O'Brien, T. P., Sawusch, M. R., Dick, J. D., and Gottsch, J. D.: Topical ciprofloxacin treatment of *Pseudomonas* keratitis in rabbits. Arch. Ophthalmol. 106:1444, 1988.

13. Reidy, J. J., Hobden, J. A., Hill, J. M., Forman, K., and O'Callaghan, R. J.: The efficacy of topical ciprofloxacin and norfloxacin in the treatment of experimental *Pseudomonas* keratitis. Cornea 10:25, 1991.

14. Palmer, M. L., and Hyndiuk, R. A.: Contact lens-related infectious keratitis. Curr. Op. Infect. Dis. 3:542, 1990.

15. Koidou-Tsiligianni, A., Alfonso, E., and Forster, R. K.: Ulcerative keratitis associated with contact lens wear. Am. J. Ophthalmol. 108:64, 1989.

16. Laibson, P. R., and Donnenfeld, E. D.: Corneal ulcers related to contact lens use. Int. Ophthalmol. Clin. 26:3, 1986.

17. Roussel, T. J., Osato, M. S., Robinson, N. M., and Wilhelmus, K. R.: Resistant *Pseudomonas* keratitis. J. Ocul. Therap. Surg. 3:136, 1984.

18. Gelender, H., and Rettich, C.: Gentamicin-resistant *Pseudomonas aeruginosa* corneal ulcers. Cornea 3:21, 1984.

19. Borrmann, L. R., and Leopold, I. H.: The potential use of quinolones in future ocular antimicrobial therapy. Am. J. Ophthalmol. 106:227, 1988.

20. Chin, N.-X., and Neu, H. C.: Post-antibiotic suppressive effect of ciprofloxacin against gram-positive and gram-negative bacteria. Am. J. Med. 82:58, 1987.

21. Hooper, D. C., Wolfson, J. S., Ng, E. Y., and Swartz, M. N.: Mechanisms of action and resistance to ciprofloxacin. Am. J. Med. 82(suppl 4A):12, 1987.

22. Smith, J. T.: The mode of action of 4-quinolones and possible mechanism of resistance. J. Antimicrob. Chemother. 18(suppl D):21, 1986.

23. Kaatz, G. W., and Seo, S. M.: Mechanism of ciprofloxacin resistance in *Pseudomonas aeruginosa*. J. Infect. Dis. 158:537, 1988.

Antibacterial Effectiveness of Ciprofloxacin 0.3% Ophthalmic Solution in the Treatment of Bacterial Conjunctivitis

Howard M. Leibowitz, M.D.

Two hundred eighty-eight cases of culture-proven bacterial conjunctivitis were evaluated as part of two multicentered, randomized, prospective clinical studies comparing the antibacterial efficacy of topically administered ciprofloxacin 0.3% either with a placebo or with tobramycin 0.3%. In the first study, ciprofloxacin was significantly ($P < .001$) more effective than the placebo. It eradicated or reduced the various bacterial pathogens in 93.6% of patients, compared to 59.5% for the placebo. In the second study, ciprofloxacin (94.5%) and tobramycin (91.9%) were equally effective. Topically applied ciprofloxacin eradicated or reduced all isolated bacterial species, attesting to its broad antibacterial spectrum and its potential usefulness in treating external ocular infections.

BACTERIAL KERATITIS is far more serious, potentially more devastating to the eye, and much more difficult to treat than bacterial conjunctivitis. Indeed, it is widely believed that many cases of conjunctivitis are self-limited and will clear without treatment. Ciprofloxacin's demonstrated effectiveness in eradicating pathogenic organisms from cases of bacterial keratitis[1] suggests that this antibiotic would similarly be highly effective in the treatment of bacterial conjunctivitis. Data from multicenter clinical studies support this conclusion.

Study Design

Two multicenter, prospective, double-masked, randomized clinical studies were carried out to determine the antibacterial efficacy of topically administered ciprofloxacin 0.3% ophthalmic solution in the treatment of acute bacterial conjunctivitis. In the first study, the effectiveness of ciprofloxacin 0.3% was compared with a placebo (ciprofloxacin vehicle); in the second study, ciprofloxacin 0.3% was compared with tobramycin 0.3%. In both studies, patients were serially cultured by separately swabbing the inferior conjunctival fornix and lower eyelid margin before the initiation of therapy and on the day after completion of therapy. Culture specimens were collected by using calcium alginate swabs, and they were transported to the laboratory in a non-nutritive balanced salt solution. The elapsed time between collection of the culture specimen and plating of the swab in the laboratory did not exceed four hours.

Qualitative and quantitative microbiologic analyses were carried out on all culture swabs by using a modification of the technique of Cagle and Abshire.[2] Threshold values were set for groups of organisms to reduce the likelihood of basing culture-positivity on the recovery of low numbers of transient organisms, the recovery of organisms, or both, that had permanently colonized the area and were not involved in an acute infectious process. Cultures from subjects with no apparent ocular bacterial infection also were analyzed to support the concept of threshold levels. These threshold values (Table 1) were used as reference points to define the microbiologic outcome as being eradication, reduction, persistence, or proliferation of the causal organism. Definitions for each of these terms are presented in Table 2. In each instance, the outcome verdict considered

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TABLE 1
THRESHOLD CRITERIA FOR JUDGING CULTURE POSITIVE SPECIMENS*

- Group 1—Threshold = 1 CFU/ml
  - *Streptococcus*, Group A, beta hemolytic (*St. pyogenes*)
  - *St. pneumoniae*
  - *Citrobacter* sp.
  - *Enterobacter* sp.
  - *Escherichia* sp.
  - *Klebsiella* sp.
  - *Proteus/Morganella* sp.
  - *Serratia marcescens*
  - Other Enterobacteriaceae
  - *N. gonorrhoeae*
  - Other *Neisseria* sp.
  - Other *Moraxella* sp.
  - *Acinetobacter* sp.
  - *Achromobacter* sp.
  - *Haemophilus* sp.
  - *Pseudomonas aeruginosa*
  - Other *Pseudomonas* sp.
- Group II—Threshold = 10 CFU/ml
  - *Staphylococcus aureus*
  - *Streptococcus* Group B (beta or nonhemolytic)
  - *Streptococcus* Group C (alpha, beta, or nonhemolytic)
  - Other *Streptococcus* (Groups D, G; nongrouped; *viridans*)
  - *Moraxella (Branhamella) catarrhalis*
- Group III—Threshold = 100 CFU/ml
  - *S. epidermidis*
  - Other coagulase-negative *Staphylococcus* sp.
  - *Micrococcus* sp.
  - *Bacillus* sp.
- Group IV—Threshold = 1000 CFU/ml
  - *Corynebacterium* (diphtheroids)

*An ocular specimen was considered culture-positive if the colony count equalled or exceeded the threshold value.

TABLE 2
DEFINITIONS FOR THE EVALUATION OF ANTIBACTERIAL EFFICACY

Eradication (E)	Infecting organism originally present above threshold on Day 0 and absent in follow-up culture.
Reduction (R)	Infecting organism originally present above threshold on Day 0 and reduced to a count below threshold in follow-up culture.
Persistence (NC)	Infecting organism originally present above threshold on Day 0 and reduced below Day 0 count (but remains above or equal to threshold) in follow-up culture.
Proliferation (P)	Infecting organism originally present above threshold on Day 0 and is increased above Day 0 count in follow-up culture.

all infecting organisms for a given site. Thus, if two infecting organisms were identified in the conjunctival culture from a given eye and only one was eradicated after treatment while the other persisted, the verdict for that eye was persistence. An outcome of eradication or reduction was considered a bacteriological cure.

Each patient in the placebo-controlled study received the coded medication for three days, and was examined clinically on day 0 (the day the patient was first seen), day 1 (the first full day of treatment) and day 3. Each patient in the tobramycin-controlled study received the coded medication for seven days and was examined clinically on days 0, 3 (optional visit), and 7. Only patients who had received neither antimicrobial nor anti-inflammatory medications during the previous 48 hours qualified for enrollment. In the placebo-controlled study, 1 or 2 drops were instilled in the affected eye every two hours while the patient was awake on days 0 and 1, and every four hours while awake on day 2. In the tobramycin-controlled study, 1 or 2 drops were instilled every two hours while the patient was awake on days 0 and 1, and every four hours while awake on days 2 through 6 inclusive. In both studies, no medications were instilled after 10:00 P.M. on the last day of therapy. An interval of at least 12 hours elapsed between the last dose of medication and the final culture.

Results

Culture specimens were obtained from 789 patients. Of these, cultures in 330 patients (42%) were positive for bacterial pathogens; 288 patients (37%) met all clinical criteria for study evaluation. Five hundred one patients were excluded for various reasons (Table 3).

The conjunctival isolates from the 288 patients meeting all clinical criteria for the study are listed in Table 4. Staphylococci were the most frequently isolated organisms (69%), followed by various gram-negative bacteria (34%), *Streptococcus* Group D, G or *St. viridans* (16%), *St. pneumoniae* (7%), and other gram-positive organisms (10%). (Values total more than 100% because more than one pathogen was isolated from some patients.)

TABLE 3
DEMOGRAPHIC SUMMARY

	TREATMENT GROUP		
	CIPROFLOXACIN	TOBRAMYCIN	PLACEBO
Patients Enrolled (N = 789)	390	311	88
Qualified Patients (N = 288)	140	111	37
Patients Excluded (N = 501)	250	200	51
Exclusion reasons			
Culture-negative	216	176	50
Unacceptable transport time	9	7	0
Final culture collection too close to last instillation of antibiotic	4	1	0
No final follow-up visit	8	5	1
Final follow-up visit outside of allowable range	9	6	0
No final culture taken	4	5	0

TABLE 4
BACTERIAL PATHOGENS ISOLATED ON DAY 0

	TREATMENT GROUP			
ORGANISM	CIPROFLOXACIN	TOBRAMYCIN	PLACEBO	TOTAL
S. aureus	38	43	15	96
S. epidermidis	40	26	18	84
Streptococcus, Group D, G, or *viridans*	25	19	2	46
Haemophilus sp.	15	10	1	26
Acinetobacter sp.	14	6	2	22
Corynebacterium sp.	13	7	0	20
Staphylococcus, coagulase-negative	10	8	1	19
St. pneumoniae	9	8	2	19
Proteus/Morganella sp.	2	13	0	15
Enterobacter sp.	4	3	1	8
Neisseria sp.	5	1	0	6
P. aeruginosa	3	2	0	5
Other *Pseudomonas* sp.	3	1	0	4
Bacillus sp.	2	1	0	3
Moraxella sp.	2	1	0	3
Micrococcus sp.	1	2	0	3
Streptococcus, Group A	2	0	0	2
Citrobacter sp.	0	2	0	2
Escherichia sp.	0	1	1	2
Eikenella corrodens	1	0	0	1
Serratia marcescens	1	0	0	1
Streptococcus, Group C	1	0	0	1
Klebsiella sp.	0	1	0	1
Moraxella (Branhamella) catarrhalis	0	0	1	1
Streptococcus, Group B	0	1	0	1
Total*	40	111	37	288

*Totals from each column are not additive because some patients were infected by more than one organism.

The overall effectiveness of each agent on all isolated bacterial species is summarized in Table 5. There was a statistically significant difference ($P < .001$) in antibacterial efficacy on day 3 between ciprofloxacin and placebo. Ciprofloxacin eradicated or reduced the various bacterial species in 93.6% of the patients, compared to 59.5% for the placebo. In the second study, ciprofloxacin and tobramycin were both highly effective; on day 7, there was no statistically significant difference ($P > .05$) between the two antibiotics in their ability to eradicate or reduce pathogenic bacteria from patients with bacterial conjunctivitis. Ciprofloxacin was effective in 94.5% of the patients, tobramycin in 91.9%.

The efficacy of ciprofloxacin 0.3% against each of the isolated bacterial species treated is shown in Table 6. These data verify the broad spectrum of antibacterial effectiveness of this agent when administered topically to treat an external ocular infection.

TABLE 5
EFFICACY AGAINST BACTERIAL CONJUNCTIVAL PATHOGENS

	CIPROFLOXACIN	TOBRAMYCIN	PLACEBO
EFFICACY	NO. (%)	NO. (%)	NO. (%)
Eradication	107 (76.4)	89 (80.2)	11 (29.7)
Reduction	25 (17.9)	13 (11.7)	11 (29.7)
Persistence	6 (4.3)	7 (6.3)	12 (32.4)
Proliferation	2 (1.4)	2 (1.8)	3 (8.1)
Total patients	140 (100)	111 (100)	37 (100)

Discussion

Conjunctivitis is a common, external ocular infection that can be caused by many types of microorganisms, among them bacteria. The infection generally is not severe, and the physician generally does not consider conjunctivitis as a serious disease. As a result, cultures are not routinely obtained.

A number of morphologic signs have been described in the inflamed conjunctiva, and many of these signs, either singly or in certain combinations, have been accorded special etiologic importance.[3] However, a previous prospective clinical study demonstrated that the etiologic diagnosis made on the basis of the initial clinical examination correlated poorly with the results of standard laboratory tests, including bacterial culture, used to establish and support a definitive etiologic diagnosis.[4] Under the best of circumstances, clinical morphologic signs and routine laboratory tests fail to produce a verified etiologic diagnosis in a substantial number of cases.

This was confirmed by the present studies: bacterial culture was negative in 442 of 789 (56%) cases initially diagnosed clinically as bacterial conjunctivitis. Although several factors may account for the negative culture, a certain unknown number surely represents an incorrect clinical diagnosis. In any event, neither the true incidence of a bacterial cause among all cases of conjunctivitis nor the causal agent of a specific case generally is known.

With certain limited exceptions (for example, hyperacute conjunctivitis caused by *Neisseria gonorrhoeae*, chronic conjunctivitis secondary to dacryocystitis or blepharitis), bacterial conjunctivitis is treated by topical application of an antibiotic at its commercially available strength. The antibiotic removes the pathogenic organisms, prevents spread of the infection to adjacent structures, lessens the intensity of inflammation, reduces morbidity, and shortens the course of the disease, returning the patient earlier to productive activities. It is also common clinical practice to treat many forms of conjunctivitis, when the origin is unknown, with a topical antibiotic preparation. Surprisingly, for reasons that are unclear, this approach often appears to be beneficial in the management of presumed nonbacterial conjunctivitis.[5] The patient is more comfortable, and the course of the disease is shortened in comparison to placebo therapy or no therapy at all.

Theoretically, an attempt should be made to identify the infectious organism in all cases of suspected bacterial conjunctivitis, and the disease should be treated with a drug specific for that organism. However, this would add considerable cost and would delay the initiation of therapy until the culture results were available. As noted, most cases are not of sufficient severity to justify such an approach. Because a wide variety of bacterial pathogens cause conjunctivitis[6] and the specific causal organism in a given case generally is unknown, the entity is most commonly treated with, and usually is highly responsive to, a topically applied broad spectrum antibiotic.

The data presented here demonstrate that a short course of ciprofloxacin 0.3% is highly effective in eradicating or reducing pathogenic

TABLE 6
EFFICACY OF CIPROFLOXACIN 0.3% OPHTHALMIC SOLUTION ON CONJUNCTIVAL BACTERIAL PATHOGENS

ORGANISM	TOTAL ISOLATES	ERADICATION	REDUCTION	PERSISTENCE	PROLIFERATION
		NO. (%)	NO. (%)	NO. (%)	NO. (%)
		Gram-positive Isolates			
S. epidermidis	40	26 (65)	13 (33)	1 (2)	
S. aureus	38	31 (82)	5 (13)	1 (2)	1 (2)
Streptococcus, Group D, G, or *viridans*	25	20 (80)	3 (12)	2 (8)	
Corynebacterium sp.	13	11 (85)	2 (15)		
Staphylococcus, Coagulase-negative	10	7 (70)	3 (30)		
St. pneumoniae	9	7 (78)		1 (11)	1 (11)
Streptococcus, Group A	2	1 (50)		1 (50)	
Bacillus sp.	2	2 (100)			
Streptococcus, Group C	1				
Micrococcus sp.	1		1 (100)	1 (100)	
Subtotal	141	105 (75)	27 (19)	7 (5)	2 (1)
		Gram-negative Isolates			
Haemophilus sp.	15	15 (100)			
Acinetobacter sp.	14	14 (100)			
Neisseria sp.	5	5 (100)			
Enterobacter sp.	4	4 (100)			
P. aeruginosa	3	3 (100)			
Other *Pseudomonas* sp.	3	3 (100)			
Moraxella sp.	2	2 (100)			
Proteus/Morganella sp.	2	2 (100)			
Se. marcescens	1	1 (100)			
Eikenella corrodens	1	1 (100)			
Subtotal	50	50 (100)	0	0	0
Total	191	155 (81)	27 (14)	7 (4)	2 (17)

bacteria causing acute conjunctivitis. All isolated bacterial species were effectively controlled. Ciprofloxacin 0.3% was at least as effective as tobramycin 0.3%, a potent aminoglycoside widely used to treat ocular infections, and significantly ($P < .001$) more effective than placebo therapy. These findings support the conclusion that topical therapy with ciprofloxacin for as little as three days effectively controls the great majority of pathogenic bacteria associated with bacterial conjunctivitis.

References

1. Leibowitz, H. M.: Clinical evaluation of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial keratitis. Am. J. Ophthalmol. 112(suppl): 34S, 1991.
2. Cagle, G. D., and Abshire, R. L.: Quantitative ocular bacteriology. A method for the enumeration and identification of bacteria from the skin-lash margin and conjunctiva. Invest. Ophthalmol. Vis. Sci. 20:751, 1981.
3. Duke-Elder, S.: Conjunctiva. In System of Ophthalmology, Diseases of the Outer Eye, vol. 8, pt. 1. St. Louis, C. V. Mosby Co., 1965, pp. 59–61.
4. Leibowitz, H. M., Pratt, M. V., Flagstad, I. J., and Berrospi, A. R.: Human conjunctivitis. I. Diagnostic evaluation. Arch. Ophthalmol. 94:1747, 1976.
5. ———: Human conjunctivitis. II. Treatment. Arch. Ophthalmol. 94:1752, 1976.
6. Perkins, R. E., Kundsin, R. B., Pratt, M. V., Abrahamsen, I., and Leibowitz, H. M.: Bacteriology of normal and infected conjunctiva. J. Clin. Microbiol. 1:147, 1980.

Clinical Evaluation of Ciprofloxacin 0.3% Ophthalmic Solution for Treatment of Bacterial Keratitis

Howard M. Leibowitz, M.D.

A multicenter, prospective clinical study of 148 culture-proven cases of bacterial keratitis, treated with ciprofloxacin 0.3% ophthalmic solution, compared its clinical and antibacterial efficacy with the standard therapy regimen of each investigator. Most often, this consisted of topically administered fortified cefazolin (33 mg/ml) and fortified gentamicin or tobramycin (14 mg/ml). Two control groups were studied: (1) patients treated while the ciprofloxacin study was ongoing (not enrolled group); and (2) patients treated during the year before initiation of the ciprofloxacin study (historical group).

Treatment with ciprofloxacin yielded a 91.9% success rate. Standard therapy yielded an 88.2% success rate among not enrolled control patients and an 88.3% success rate among the historical control patients. No serious side effects accompanied ciprofloxacin administration. In vitro susceptibility testing showed ciprofloxacin to be highly effective against bacterial corneal pathogens. These findings suggest that ciprofloxacin 0.3% is safe and effective as a single agent for the treatment of bacterial keratitis.

THE FIRST fluoroquinolone commercially available in the United States as a topical ophthalmic formulation is ciprofloxacin 0.3% (Ciloxan, Alcon Laboratories, Ft. Worth, Texas). Ciprofloxacin is effective in vitro against *Staphylococcus aureus* and coagulase-negative staphylococci, against *Streptococcus pneumoniae* and *St. pyogenes*, against *Neisseria gonorrhoeae, Haemophilus* and *Moraxella* and against most enteric gram-negative bacilli including *Pseudomonas aeruginosa*.[1,2] It is also effective in vitro against many strains of *Mycobacteria*, including *My. tuberculosis*, and against *Chlamydia trachomatis*.[1,2]

The forgoing organisms constitute the great majority of pathogens incriminated in the origin of bacterial keratitis,[3-5] suggesting that ciprofloxacin might be highly effective in the treatment of this disorder. Consequently a multi-institutional clinical study was conducted to test this hypothesis. This is the first large-scale study in the United States in which a single antibiotic was used to treat bacterial keratitis and in which the antibiotic was used at its commercial concentration. In no instance was the concentration of ciprofloxacin increased or fortified above 0.3% (3 mg/ml).

Study Design

A multicenter, prospective, open-label study was carried out from Aug. 1, 1989, to Oct. 16, 1990, to determine the following: (1) the clinical and antibacterial efficacy of topically administered ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial keratitis, and (2) the in vitro susceptibility to ciprofloxacin of bacterial organisms isolated from cases of bacterial keratitis. Thirty-three investigators, listed at the end of this article, obtained the approval of their Investigational Review Boards and participated in the study. The investigators were divided into two groups on the basis of geographical distribution. With minor exceptions, those located east of the Mississippi River carried out Study I; those west of the Mississippi River carried out Study II. This ensured that the study had sufficient patient enrollment for evaluation of ciprofloxacin efficacy and safety

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and that it addressed any differences among bacterial pathogens and their susceptibility to antibiotics in various sections of the country. The results of the two studies showed no statistical difference for gender, race, age of the patient, days on therapy or diameter of the corneal ulcer at manifestation. Therefore, the data from the two studies were combined for evaluation.

A total of 210 patients (210 eyes) were included. The criterion for enrollment was simply presumed bacterial corneal ulcer on clinical examination. However, among the enrolled patients, only those who met the following criteria were examined to establish drug efficacy:

A. Corneal scrapings were obtained from each of the presumed bacterial corneal ulcers before the initiation of therapy. A patient had to have an initial culture (day 0) that was positive for bacteria only. Mixed bacterial-fungal cultures were not evaluated for drug efficacy.

B. There could be no additional antibacterial or antifungal agents used to treat the patient in conjunction with ciprofloxacin.

C. The patient had to be dosed according to the prescribed treatment protocol.

D. The patient had to have a final examination by a physician to ensure that clinically the infection had been eradicated.

Of the original 210 enrolled eyes, 148 met the criteria for evaluation of drug efficacy (Table 1).

TABLE 1
DISTRIBUTION OF PATIENTS

	NO. ENROLLED	EVALUATED FOR DRUG EFFICACY NO. (%)	NOT EVALUATED FOR DRUG EFFICACY NO. (%)
	Ciprofloxacin-treated		
Study I	131	86 (66)	45 (34)
Study II	79	62 (78)	17 (22)
Total	210	148 (70)	62 (30)
	Controls		
Not enrolled	81	51 (63)	30 (37)
Historical	147	103 (70)	44 (30)

TABLE 2
CIPROFLOXACIN DOSING REGIMEN

Day 0	(Day patient was first seen) (a) 2 drops every 15 min for 6 hrs, then (b) 2 drops every 30 min for the remainder of the day
Day 1	2 drops every hr
Days 2 to 14	2 drops every 4 hrs
After Day 14	At the discretion of the treating physician

Data from all 210 patients were included in the evaluation of drug safety.

The dosing regimen (Table 2) called for instillation of 2 drops of ciprofloxacin every 15 minutes for the first six hours of treatment and then 2 drops every 30 minutes for the remainder of day 0 (the day the patient was seen). On the first full day of treatment, day 1, the dosage was decreased to 2 drops every hour. From days 2 to 14, ciprofloxacin was administered at a dose of 2 drops every four hours. If treatment was required past day 14, the dosing regimen was at the discretion of the investigator.

Clinical observations were recorded on a standardized case report form on day 0, day 1, day 3 (±1), day 7 (±2), and day 14 (±2). If treatment was extended past day 14 (±2), additional clinical observations were recorded, including an observation at the time treatment was stopped. For most patients, the findings of an "off therapy" examination also were recorded at least one week after therapy had been discontinued.

At each clinical examination, individual ocular signs and symptoms (Table 3) were graded by using the following semi-quantitative scale: 0, not present; 1, mild; 2, moderate; and 3, severe. Each investigator was provided with a Manual of Definitions to standardize scoring among investigators. Additionally, the investigator evaluated the patient's overall clinical condition and made one of the following judgments regarding response to therapy at each visit: cured (score 0 = complete re-epithelialization, no evidence of bacterial infection and absence of symptoms and signs); improved (score 1 = complete re-epithelialization, no evidence of bacterial infection and a unit change of improvement in two or more symptoms or signs); unchanged (score 2 = incomplete re-epithelialization, evidence of bacterial infection, and no overall change in symptoms or signs); and worse (score 3 = re-epithelializa-

TABLE 3
OCULAR SYMPTOMS AND SIGNS

- Ocular symptoms evaluated
  - Discomfort
  - Acute pain
  - Tearing
  - Photophobia
  - Itching
- Ocular signs evaluated
  - Erythema and swelling of the eyelids
  - Discharge exudate
  - Changes in bulbar conjunctiva
  - Changes in palpebral conjunctiva
  - Limbal abnormalities
  - Disorders of corneal epithelium
  - Focal infiltration of corneal stroma
  - Anterior chamber cells and flare

tion not progressing, evidence of bacterial infection and an overall increase in severity of symptoms or signs).

Three factors of drug efficacy were assessed: (1) the physician's overall clinical impression of efficacy; (2) clinical resolution of symptoms and signs; and (3) in vitro susceptibility of bacterial isolates to ciprofloxacin.

Clinical success was achieved if the physician's clinical judgment was graded as cured or improved at the last follow-up examination. Among those patients treated with ciprofloxacin, a failure included any patient who required the initiation of additional or alternative therapy. Among the control groups, the rate of clinical success was independent of the number of antibiotics in the initial regimen or their route of administration. Bacteriologic success was achieved if the offending microorganism isolated from the corneal ulcer on day 0 was shown to be susceptible to ciprofloxacin in vitro.

The results of ciprofloxacin efficacy were compared with the following: (1) data collected retrospectively by reviewing the case histories from the investigator's practice of patients with bacterial keratitis who were not enrolled in the ciprofloxacin study but who instead were treated with "standard therapy" during the same period that the ciprofloxacin study was ongoing; and (2) data collected retrospectively on patients with bacterial keratitis who were treated by the investigator with standard therapy during the year before initiating the ciprofloxacin study.

For each of these two groups, data similar to that recorded for the ciprofloxacin-treated patients were collected for each corneal ulcer treated by the investigator during the times specified; none was excluded from data analysis for any reason.

Data on the safety of ciprofloxacin ophthalmic solution 0.3% were collected on 1,520 patients who participated in the initial safety and toxicity studies of this drug as well as those who were treated with the drug as part of approved protocols evaluating its efficacy for treatment of blepharitis, conjunctivitis, and keratitis. Additionally, 450 patients with blepharitis and blepharoconjunctivitis were treated with ciprofloxacin 0.3% ophthalmic ointment and provided more safety data.

Untoward events, defined as being any significant change in the patient's ophthalmic or medical health, were encountered as solicited and unsolicited complaints from study participants, direct observations of the investigators, and a review of the case report forms. Each event was evaluated to determine its level of seriousness and to establish whether the event was related or unrelated to ciprofloxacin. Nonserious events were defined as any reported medical event that was considered by the investigator and an independent medical monitor as neither life- nor sight-threatening. Serious events were defined as any reported untoward event that was life- or sight-threatening, fatal, caused or prolonged hospitalization, was disabling, alarming, or potentially serious. The relationship of the event to ciprofloxacin therapy was assessed independently by the investigator and the medical monitor.

Results

Efficacy

Of the original 210 enrolled patients (210 eyes), 148 met the criteria for evaluation of efficacy of ciprofloxacin. The remaining 62 patients failed to meet the criteria for one of the following reasons: (1) culture-negative on day 0 (49 patients); (2) lost to follow-up (five patients); (3) received antimicrobial therapy in addition to ciprofloxacin (three patients), (4) noncompliance (three patients); and (5) mixed bacterial-fungal infection (two patients).

A total of 38 different strains of bacteria were

TABLE 4
BACTERIA ISOLATED FROM CORNEAL ULCERS

BACTERIAL ORGANISMS	NO. OF CASES
S. epidermidis	41
*S. aureus**	34
S. hominis	4
S. haemolyticus	2
S. capitis	1
S. simulans	1
S. hyicus	1
Staphylococcus coagulase-negative (nonspeciated)	8
Micrococcus sp.	3
Stomatococcus mucilaginosus	1
St. agalactiae	1
St. pneumoniae	13
St. viridans group	13
St. sanguis	8
St. mitis	1
Nonspeciated	4
Streptococcus, Group D nonenterococcus	2
Enterococcus faecalis	1
P. aeruginosa	23
P. fluorescens	2
Serratia marcescens	9
Se. liquefaciens	1
Proteus mirabilis	2
Pr. vulgaris	1
Enterobacter agglomerans	1
En. cloacae	1
Acinetobacter cloacae	1
Haemophilus influenzae	4
H. parainfluenzae	2
Moraxella lacunata	1
Mo. (Branhamella) catarrhalis	1
Moraxella species (nonspeciated)	2
Capnocytophaga sp. (DF-1)	1
Bacillus sp.	1
Corynebacterium xerosis	1
Corynebacterium species (diphtheroids)	9
Propionibacterium acnes	9
Peptostreptococcus magnus	1
Mycobacterium chelonae	1
Total	199
Gram-positive bacteria	147 (73.9%)
Gram-negative bacteria	52 (26.1%)

*Includes 3 methicillin-resistant strains.

isolated from the 148 eyes that were evaluated for drug efficacy. The frequency with which various bacterial types were isolated is presented in Table 4. Among these isolates, 73.9% were gram-positive strains and 26.1% were gram-negative strains. The seven most frequently isolated bacterial types were *Staphylococcus epidermidis*, *S. aureus*, *Pseudomonas aeruginosa*, *Streptococcus viridans* group, *St. pneumoniae*, *Serratia marcescens*, and *Propionibacterium acnes*.

Final grading of ciprofloxacin efficacy was carried out clinically and defined as follows:

A grading of "cured" required complete re-epithelialization of the infected cornea and the absence of staining of the corneal surface. There could be no evidence of active bacterial infection, and examination disclosed an absence of clinical symptoms and signs.

A grading of "improved" also required complete re-epithelialization of the infected cornea, no clinical evidence of persistent bacterial infection, and a substantial decrease in the severity of at least two or more symptoms and signs.

A grading of "unchanged" reflected incomplete re-epithelialization, evidence of bacterial infection, and no overall change in symptoms or signs.

A grading of "worse" reflected the failure of re-epithelialization to progress, evidence of bacterial infection, and an overall increase in the severity of symptoms or signs.

The grades for cured and improved were combined and defined as "clinical success." Thus, clinical success was achieved if, in the physician's clinical judgment, the patient was graded as either cured or improved at the final visit, since by definition, the infection had resolved and complete re-epithelialization of the cornea had occurred in both categories. Using this grading system, we achieved a 91.9% clinical success with topical ciprofloxacin therapy (Table 5).

Among the 49 patients with the initial clinical diagnosis of bacterial corneal ulcer but in whom the corneal culture was negative, 45 had follow-up examinations. Of these patients, forty (89%) were assessed as clinically successful (cured or improved) after treatment with ciprofloxacin ophthalmic solution.

The data were analyzed to determine the effectiveness of ciprofloxacin in cases of bacterial keratitis of varying severity. No significant differences were observed; the rate of clinical success among mild, moderate, and severe cases was essentially the same. Data on the clinical outcome vs initial ulcer diameter are shown in Table 6. Data on the efficacy of ci-

TABLE 5
DRUG EFFICACY

		CURED	IMPROVED	UNCHANGED	WORSE	CLINICAL SUCCESS*
TREATMENT	NO.	NO. (%)	NO. (%)	NO. (%)	NO. (%)	NO. (%)
Ciprofloxacin 0.3%	148	113 (76.3)	23 (15.5)	6 (4.1)	6 (4.1)	136 (91.99)
Not enrolled (Standard therapy)	51	33 (64.7)	12 (23.5)	4 (7.8)	2 (3.9)	45 (88.2)
Historical (Standard therapy)	103	65 (63.1)	26 (25.2)	6 (5.8)	6 (5.8)	91 (88.3)

*Clinical success = cured and improved.

profloxacin against some commonly encountered individual pathogens are summarized in Table 7.

Twelve (8.1%) patients did not respond to ciprofloxacin ophthalmic solution ("unchanged" or "worse") and were considered treatment failures (Table 5). All but one organism isolated from these patients were sensitive to ciprofloxacin in vitro (Table 8). In four patients, the cornea was infected by more than one bacterium. The single resistant isolate (*Mycobacterium chelonae*) was isolated from a polymicrobic infection. Two additional bacterial strains, one isolate each of *St. sanguis* and *Corynebacterium* species, were resistant in vitro to a concentration of < 3.0 μg/ml of ciprofloxacin. However, the in vivo response in both of these patients was judged to be a clinical success.

Each investigator evaluated, graded the severity of, and recorded the data on five symptoms (ocular discomfort, acute ocular pain, tearing, photophobia, and itching) for each patient at the completion of each examination. Similarly, eight signs (erythema and swelling of the eyelids, conjunctival discharge/exudate, changes in the bulbar conjunctiva, changes in the palpebral conjunctiva, limbal abnormalities, disorders of the corneal epithelium, focal infiltrates of the corneal stroma, and anterior chamber flare and cells) were evaluated and graded, and the data recorded for each patient at the completion of each examination. The mean scores for the severity of the five symptoms and eight signs were tabulated (Table 9). These data show a progressive resolution of symptoms and signs under treatment with ciprofloxacin and support the effectiveness of treatment with this antibiotic.

Of the 148 patients examined for drug effica-

TABLE 6
CLINICAL SUCCESS VS INITIAL ULCER DIAMETER

		CURED	IMPROVED	UNCHANGED	WORSE		CLINICAL SUCCESS*
ULCER SIZE	TREATMENT	NO. (%)	NO. (%)	NO. (%)	NO. (%)	TOTAL NO.	NO. (%)
<2 mm	Ciprofloxacin	33 (78.6)	4 (9.5)	3 (7.1)	2 (4.8)	42	37 (88.1)
	Historical	10 (100)	0	0	0	10	
2-4 mm	Ciprofloxacin	49 (77.8)	13 (20.6)	0	1 (1.6)	63	62 (98.4)
	Historical	36 (62.1)	15 (25.9)	4 (6.9)	3 (5.2)	58	51 (88.0)
>4 mm	Ciprofloxacin	31 (72.1)	6 (14.0)	3 (7.0)	3 (7.0)	43	37 (86.1)
	Historical	18 (52.9)	11 (32.4)	2 (5.9)	3 (8.8)	34	29 (85.3)
Total	Ciprofloxacin	113 (76.4)	23 (15.5)	6 (4.1)	6 (4.1)	148	136 (91.9)
	Historical	64 (62.7)†	26 (25.5)	6 (5.9)	6 (5.9)	102†	90 (88.2)

P = .024, Cochran-Mantel-Haenszel Rank Test, controlling for ulcer size at day 0.

*Clinical success = cured and improved.

†Ulcer size for one historical patient rated "cured" was not reported.

cy, 120 were examined at least one week after discontinuation of ciprofloxacin therapy. All were judged to be cured or improved, suggesting that corneal ulcers do not recur after discontinuation of topical ciprofloxacin.

Data were collected on an additional 50 patients who had been unresponsive to initial therapy with other antibiotics and subsequently were treated with topical ciprofloxacin 0.3%. The clinical outcome of ciprofloxacin therapy was excellent because the corneal ulcers resolved in 46 (92%) of these patients (Table 10).

Controls

Because of the potentially devastating nature of bacterial keratitis, we were unable to conduct a placebo-controlled, double-masked, experimental protocol. To ascertain how our results with topical ciprofloxacin therapy compared with those of conventional therapy, we compared the ciprofloxacin findings to those in two alternative control groups. The first group, referred to as "not enrolled," included those patients in whom bacterial keratitis was diagnosed and who were treated by the investigator with standard therapy during the same period that the ciprofloxacin study was ongoing. These patients were not enrolled for a variety of reasons: (1) the patient failed to volunteer for an experimental study; (2) the patient was monocular and therefore precluded from enrollment by our experimental protocol; (3) the infection was related to an industrial accident and anticipated legal entanglements made it unwise to include the patient in an experimental study; (4) antibiotics other than ciprofloxacin had been instilled before the patient was seen by the investigator; and (5) the investigator was not available to enroll the patient at the time the patient was first seen.

A total of 81 patients with bacterial keratitis treated by the participating investigators were not enrolled in the ciprofloxacin protocol while the study was underway. Fifty-one patients had a positive bacterial culture on day 0 and otherwise met the criteria for evaluation of drug efficacy (Table 1). Patients in this "not enrolled" group were treated with whatever form of therapy the investigator considered standard. Most received fortified cefazolin at a concentration of 33 mg/ml along with fortified

TABLE 7
CIPROFLOXACIN EFFICACY AGAINST SELECTED PATHOGENS

		CURED	IMPROVED	UNCHANGED	WORSE	CLINICAL SUCCESS
TREATMENT	ORGANISM	NO. (%)	NO. (%)	NO. (%)	NO. (%)	NO. (%)
Ciprofloxacin 0.3%	*P. aeruginosa*	20 (87.0)	1 (4.3)	—	2 (8.7)	21 (91.3)
	S. epidermidis	32 (76.2)	8 (19.0)	1 (2.4)	1 (2.4)	40 (95.2)
	S. aureus	26 (74.3)	4 (11.4)	3 (8.6)	2 (5.7)	30 (85.7)
	St. pneumoniae	7 (53.8)	3 (23.1)	1 (7.7)	2 (15.4)	10 (76.9)
	All other bacteria	54 (78.3)	11 (15.9)	3 (4.3)	1 (1.4)	65 (94.2)
Not enrolled (Standard)	*P. aeruginosa*	3 (75.0)	—	1 (25.0)	—	3 (75.0)
	S. epidermidis	3 (75.0)	—	1 (25.0)	—	3 (75.0)
	S. aureus	6 (54.5)	5 (45.5)	—	—	11 (100)
	St. pneumoniae	2 (50.0)	1 (25.0)	—	1 (25.0)	3 (75.0)
	All other bacteria	23 (69.7)	7 (21.2)	2 (6.1)	1 (3.0)	30 (90.9)
Historical (Standard)	*P. aeruginosa*	9 (81.8)	2 (18.2)	—	—	
	S. epidermidis	8 (61.5)	3 (23.1)	1 (7.7)	1 (7.7)	
	S. aureus	9 (56.3)	6 (37.5)	1 (6.3)	—	
	St. pneumoniae	6 (66.7)	3 (33.3)	—	—	
	All other bacteria	37 (59.7)	15 (24.2)	5 (8.1)	5 (8.1)	

*Four of the 11 *P. aeruginosa* cases (36%) were initial treatment failures and required additional attimicrobial therapy to effect clinical success.

TABLE 8
CLINICAL FAILURES ON CIPROFLOXACIN TREATMENT

PATIENT NO.	ORGANISM	IN VITRO SUSCEPTIBILITY TO CIPROFLOXACIN
1	*P. aeruginosa*	Yes
	S. aureus	Yes
2	*St. pneumoniae*	Yes
3	*S. epidermidis*	Yes
	S. haemolyticus	Yes
4	*P. aeruginosa*	Yes
5	*S. aureus*	Yes
6	*S. aureus*	Yes
	St. pneumoniae	Yes
7	*M. chelonae*	No
	S. epidermidis	Yes
	P. acne	Yes
8	*S. aureus*	Yes
9	*St. pneumoniae**	Yes
10	*S. aureus*	Yes
11	*S. epidermidis*	Yes
12	*S. epidermidis*	Yes

*HIV-positive.

gentamicin or tobramycin at a concentration of 1.4%. However, some patients received other fortified antibiotics or treatment in addition to topical fortified antibiotics. Some received subconjunctival injections of antibiotics, and a few also received systemic antibiotics. The overall success rate among the "not enrolled" patient group was 88.2%, not statistically significantly different from the ciprofloxacin group (Table 5).

We also examined a second group of controls whom we referred to as "historical controls." These patients had bacterial keratitis treated by the investigator in the year before initiation of the ciprofloxacin study. Again, treatment consisted of the investigator's standard mode of therapy and was essentially the same as the "not enrolled" group of controls, primarily topically administered fortified cefazolin and an aminoglycoside. A total of 147 cases were collected of which 103 met the criteria of the ciprofloxacin study for evaluation of drug efficacy (Table 1). The results were almost identical to those obtained in the "not enrolled" group, with an 88.3% overall success rate (Table 5).

Significantly more initial treatment failures were reported among the "not enrolled" patient group (14/51 [27.5%]; $P = .005$ Mantel-Haenszel Chi-Square Test) and "historical" patient group (36/103 [35.0%]; $P < .001$ Mantel-Haenszel Chi-Square Test) than among patients treated with ciprofloxacin. A patient in the two control groups was considered a treatment failure if, after initial therapy, additional therapy was required because of a lack of adequate clinical response. A comparison of the duration of treatment with ciprofloxacin and standard therapy (Table 11) shows a definite trend toward a shorter treatment interval with ciprofloxacin. Although the difference between the ciprofloxacin-treated group and the "not enrolled" controls failed to reach statistical significance ($P > .05$), the difference between the ciprofloxacin-treated group and the "historical" controls was highly significant ($P < .001$).

Microbiology

The results of in vitro susceptibility testing show ciprofloxacin to be effective against the most frequently encountered organisms isolated from cases of bacterial keratitis: *S. aureus, P. aeruginosa, S. epidermidis,* and *St. pneumoniae.*

TABLE 9
MEAN SCORE OF THE AVERAGE OF OCULAR SYMPTOMS AND SIGNS IN RESPONSE TO TOPICAL ADMINISTRATION OF CIPROFLOXACIN 0.3%

	STUDY I			STUDY II		
DAY	NO.	SYMPTOMS	SIGNS	NO.	SYMPTOMS	SIGNS
0	86	1.39 (±0.48)	1.59 (±0.59)	61	1.70 (±0.49)	1.78 (±0.53)
1	86	1.09 (±0.53)	1.47 (±0.57)	59	1.23 (±0.44)	1.51 (±0.51)
3	84	0.81 (±0.54)	1.22 (±0.61)	59	0.85 (±0.52)	1.10 (±0.53)
7	79	0.53 (±0.42)	0.90 (±0.56)	56	0.54 (±0.50)	0.72 (±0.52)
14	78	0.35 (±0.42)	0.59 (±0.52)	53	0.32 (±0.43)	0.38 (±0.41)
Off therapy	62	0.10 (±0.26)	0.10 (±0.25)	42	0.15 (±0.37)	0.11 (±0.34)

TABLE 10
OUTCOME OF CASES OF BACTERIAL KERATITIS UNRESPONSIVE TO STANDARD THERAPY AND SUBSEQUENTLY TREATED WITH CIPROFLOXACIN

ORGANISM ISOLATED FROM CORNEA	INITIAL TREATMENT	OUTCOME WITH CIPROFLOXACIN THERAPY
Single Organism		
S. aureus	Cefazolin, gentamicin	Cured
S. aureus	Vancomycin	Improved
S. aureus	Cefazolin	Cured
S. aureus	Tobramycin, gentamicin	Cured
S. aureus	Tobramycin	Cured
S. aureus	Sisomycin, tobramycin	Cured
S. aureus	Gentamicin	Cured
S. aureus	Neosporin, tobramycin	Cured
S. aureus	Tobramycin	Cured
S. epidermidis	Tobramycin	Cured
S. epidermidis	Sodium sulfacetamide	Improved
S. epidermidis	Norfloxacin	Cured
S. epidermidis	Norfloxacin	Improved
S. epidermidis	Gentamicin	Improved
S. epidermidis	Tobramycin, Polytrim	Cured
S. epidermidis	Bacitracin, neomycin, polymyxin B	Cured
S. epidermidis	Erythromycin	Cured
S. epidermidis	Vancomycin	Unchanged
S. hominis	Cefazolin, gentamicin	Improved
St. pneumoniae	Chloramphenicol	Improved
St. pneumoniae	Cefazolin, gentamicin	Cured
St. viridans	Cefazolin, bacitracin	Cured
St. sanguis	Neosporin	Cured
St. sanguis	Choramphenicol	Unchanged
St. agalactiae	Tobramycin	Cured
P. aeruginosa	Gentamicin	Cured
P. aeruginosa	Cefazolin, gentamicin, Neosporin	Cured
P. aeruginosa	Cefazolin, gentamicin, Neosporin	Cured
P. aeruginosa	Cefazolin, gentamicin	Cured
P. aeruginosa	Cefazolin, chloramphenicol	Cured
P. aeruginosa	Tobramycin	Cured
P. aeruginosa	Tobramycin	Cured
P. aeruginosa	Tobramycin	Cured
P. aeruginosa	Bactrim	Cured
H. influenza	Norfloxacin, tobramycin	Cured
Se. marcescens	Neosporin	Cured
P. acnes	Gentamicin	Improved
P. acnes	Bacitracin, polymycin, tobramycin, doxycycline	Cured
Polymicrobic		
S. epidermidis + *S. haemolyticus*	Cefazolin, gentamicin	Unchanged
S. epidermidis + *S. aureus*	Tobramycin	Improved
S. haemolyticus + *S. aureus*	Polysporin	Improved
P. aeruginosa + *P. acnes*	Bacitracin, gentamicin	Cured
M. chelone + *S. epidermidis* + *P. acnes*	Amikacin	Worse
P. acnes + *S. epidermidis*	Tobramycin	Cured
Moraxella species + Group D *Streptococcus* + *Micrococcus* species	Cefazolin	Cured
H. influenza + *S. epidermidis*	Gentamicin	Cured
P. aeruginosa + Coagulative-negative *Staphylococcus*	Cefazolin, tobramycin	Cured
St. sanguis + *P. fluorescens*	Polysporin, tobramycin	Cured

All of the tested isolates except three were susceptible in vitro to < 3.0 μg/ml of ciprofloxacin. The three exceptions were one isolate each of *M. chelonae, St. sanguis*, and *Corynebacterium* species. The cornea infected with *M. chelonae* was a treatment failure, but the other two (*S. sanguis* and *Corynebacterium* sp.) were treated successfully with topical ciprofloxacin (cure), demonstrating once again that in vitro microbiologic results do not always correlate with clinical outcome (Table 12).

Safety

Untoward ocular events related, or possibly related, to ciprofloxacin therapy were all mild, nonserious in nature, and resolved without treatment. Among the 210 corneal ulcer patients enrolled in this study, 53 untoward events were encountered in 46 patients (Table 13).

The most frequently noted untoward ocular event associated with ciprofloxacin therapy was a white crystalline precipitate commonly located in the superficial portion of the corneal defect (Figure). This phenomenon was encountered in 35 patients. In 25 of these patients, the precipitate was located in the area of the corneal ulcer. Twenty-eight of the precipitates were described as white and 18 were characterized as granular/crystalline. The precipitate was observed more frequently in patients older than 60 years, but it was unrelated to the gender of the patient, the organism cultured, the size or stromal depth of the ulcer or infiltrate, or the time to resolution. Samples of the precipitate, obtained from the corneal ulcers of patients, were analytically shown to be ciprofloxacin. The exact factors contributing to the formation of the ciprofloxacin precipitate are unknown.

The precipitate first appeared within one to seven days after initiating therapy. In some cases it resolved despite continued therapy. Early in the study, before any information was available about the nature or significance of the precipitate, ciprofloxacin therapy was discontinued in one patient when the phenomenon was observed. In no other instance did the appearance of the precipitate preclude continued use of ciprofloxacin or prevent the patient from continuing in the study. In at least one patient, the precipitate was irrigated from the cornea and did not recur in the face of continued ciprofloxacin treatment. The precipitate did not require adjunctive therapy and, in all cases, was judged to be nonserious by the investigator and medical monitor.

TABLE 11
COMPARISON OF DURATION OF TREATMENT WITH CIPROFLOXACIN AND STANDARD THERAPY

ANTIBIOTIC REGIME	NO.	DAYS ON THERAPY	STANDARD DEVIATION	P VALUE*
Ciprofloxacin 0.3%	148	21.5	19.0	—
Not enrolled controls	51	29.9	30.2	0.07†
Historical controls	103	53.1	73.8	0.001‡

*Based on two-sample *t*-test.

†Comparison of ciprofloxacin-treated group and not enrolled control group.

‡Comparison of ciprofloxacin-treated group and historical control group.

Other untoward ocular events related, or possibly related, to therapy included discomfort, crystals on the lashes, foreign body sensation, chemosis, punctate epithelial erosion, eyelid edema, conjunctival hyperemia, worsened infiltrate, tearing, itching, and superficial punctate keratitis. Only three patients were discontinued from the study because of untoward ocular events (Table 14). All other ocular untoward events resolved on continued therapy and were judged to be nonserious.

Two nonocular untoward events related or possibly related to ciprofloxacin therapy were encountered. One patient reported bad taste and another reported nausea. These events were self-limited and resolved without treatment.

To enhance the data base on the safety of ciprofloxacin ophthalmic solution 0.3%, information on untoward ocular events, obtained from the original ocular safety and comfort studies, studies evaluating its effectiveness in blepharitis, conjunctivitis, and blepharoconjunctivitis, and a study of ciprofloxacin plasma levels after topical ocular administration, was combined with the keratitis safety data. At the time this article was prepared, safety data were available on 1,520 patients. Among patients in this larger series, the most frequently reported medical events related, or possibly related, to topical ciprofloxacin therapy were as follows: discomfort (9.7%), taste abnormality (5.0%), white precipitate (3.6%), foreign body sensation (2.0%), and itching (1.1%). All other events were reported at an incidence of less than 1.0%.

TABLE 12
IN VITRO ANTIBIOTIC SUSCEPTIBILITY OF BACTERIAL CORNEAL ISOLATES

DRUG	NO. OF STRAINS	<3.0 G/ML	>3.0 G/ML	RESISTANT ORGANISMS*
		NO. (%)	NO. (%)	
Ciprofloxacin	137	134 (98)	3 (2)	M. chelonae (1)
				Corynebacterium sp. (1)
				S. warneri (1)
Oxacillin	137	87 (64)	50 (36)	*S. aureus* (3)
				S. epidermidis (4)
				S. haemolyticus (1)
				S. warneri (1)
				P. aeruginosa (16)
				P. fluorescens (2)
				P. maltophilia (1)
				Se. marcescens (9)
				Se. liquifaciens (1)
				Citrobacter freundi (1)
				Flavobacterium indologenes (1)
				F. meningosepticum (1)
				Pr. mirabilis (1)
				H. influenzae (1)
				H. parainfluenzae (1)
				Enterobacter agglomerans (1)
				Bacillus species (1)
				Pr. mirabilis (1)
				Micrococcus species (1)
				En. cloacae (1)
				H. influenzae (1)
Tobramycin	137	97 (71)	40 (29)	*S. aureus* (7)
				S. epidermidis (11)
				S. haemolyticus (1)
				S. warneri (1)
				St. pneumoniae (2)
				St. pyogenes (1)
				St. viridans (2)
				St. mitis (1)
				St. sanguis (4)
				Streptococcus, Group D, nonenterococcus (1)
				Se. marcescens (1)
				F. indologenes (1)
				F. meningosepticure (1)
				Corynebacterium species (2)
				Mycobacterium chelonae (1)
				P. fluorescens (1)
				Micrococcus species (1)

*Resistant organisms are those resistant to a concentration of >3. ug/ml for each antibiotic tested.

TABLE 13
UNTOWARD EVENTS IN 210 PATIENTS WITH BACTERIAL KERATITIS TREATED WITH CIPROFLOXACIN OPHTHALMIC SOLUTION 0.3%

	NO.	%
Treatment-Related or Possibly Related		
Ocular		
White precipitate	35	16.6
Discomfort	4	1.9
Crystals on lashes	3	1.4
Chemosis	2	1.0
Foreign body sensation	2	1.0
Punctate epithelial erosion	1	0.5
Eyelid edema	1	0.5
Conjunctival hyperemia	1	0.5
Infiltrate worsened	1	0.5
Tearing	1	0.5
Itching	1	0.5
Superficial punctate keratitis	1	0.5
Nonocular		
Nausea	1	0.5
Bad Taste	1	0.5
Not Treatment-Related		
Ocular		
Ulcer perforated	2	1.0
Infiltrate worsened	2	1.0
Ulcer larger/deepened	2	1.0
Aqueous inflammation increased	1	0.5
Subconjunctival hemorrhage	1	0.5
Conjunctival signs worsened	1	0.5
Infection	1	0.5
Leaking descemetocele	1	0.5
Photophobia	1	0.5
Nonocular		
Flu	1	0.5
Atrial fibrillation	1	0.5
Diarrhea	1	0.5
Pregnancy	1	0.5

TABLE 14
PATIENTS WITH BACTERIAL KERATITIS IN WHOM TREATMENT WITH CIPROFLOXACIN OPHTHALMIC SOLUTION 0.3% WAS DISCONTINUED BECAUSE OF AN UNTOWARD OCULAR EVENT

REASON FOR DISCONTINUATION	NO.	TREATMENT RELATED	SERIOUS
White corneal precipitate	1	Yes	No
Infiltrate worsened*	1	No	No
Conjunctival hyperemia*	1	Possible	No

*Culture-negative for bacteria.

Discussion

Scarring of the cornea results from bacterial infection and is a cause of impaired vision. Visual loss is often preventable if the cause is determined early and appropriate treatment is begun. Antibiotics must be administered in a timely manner and in sufficient quantity to inhibit bacterial replication and to limit invasion and destruction of the corneal stroma by the causal organisms. Both gram-positive and gram-negative bacteria can cause serious infections of the cornea. Therefore, if one is to treat such infections with a single antibacterial agent, an ophthalmic antibiotic with broad spectrum activity is required. Until now, the treating ophthalmologist has not been confident that any single antibiotic had a sufficiently broad spectrum of action to allow its use as a single agent for the initial treatment of bacterial keratitis.

Most authorities recommend that bacterial keratitis initially be treated with at least two antibiotics, one predominantly effective against gram-positive organisms, the other against gram-negative organisms.[6-8] Most commonly, a cephalosporin (for example, cefazolin) is used to cover gram-positive bacterial pathogens and an aminoglycoside (for example, gentamicin or tobramycin) to cover gram-negative organisms.[6-8] Equally important, virtually all authorities have emphasized that the antibiotic concentration in commercially available formulations is insufficient to eradicate bacterial pathogens from the cornea and that these products must be formulated at significantly higher concentrations to treat bacterial keratitis effectively.[6-8] Some authorities also recommend that the use of high-dose (fortified) topical antibiotics be supplemented with antibiotics given by subconjunctival injection.[6-8]

There are obvious limitations to the aforementioned approaches to therapy. Hazards and risks of the currently recommended topical polypharmacy approach include the following: (1) contamination of sterile ingredients when extemporaneously preparing fortified antibiotics; (2) incorrect calculation of volume requirements resulting in incorrect dosages; (3) washout of one agent if a second agent is applied shortly after the first; and (4) an increased

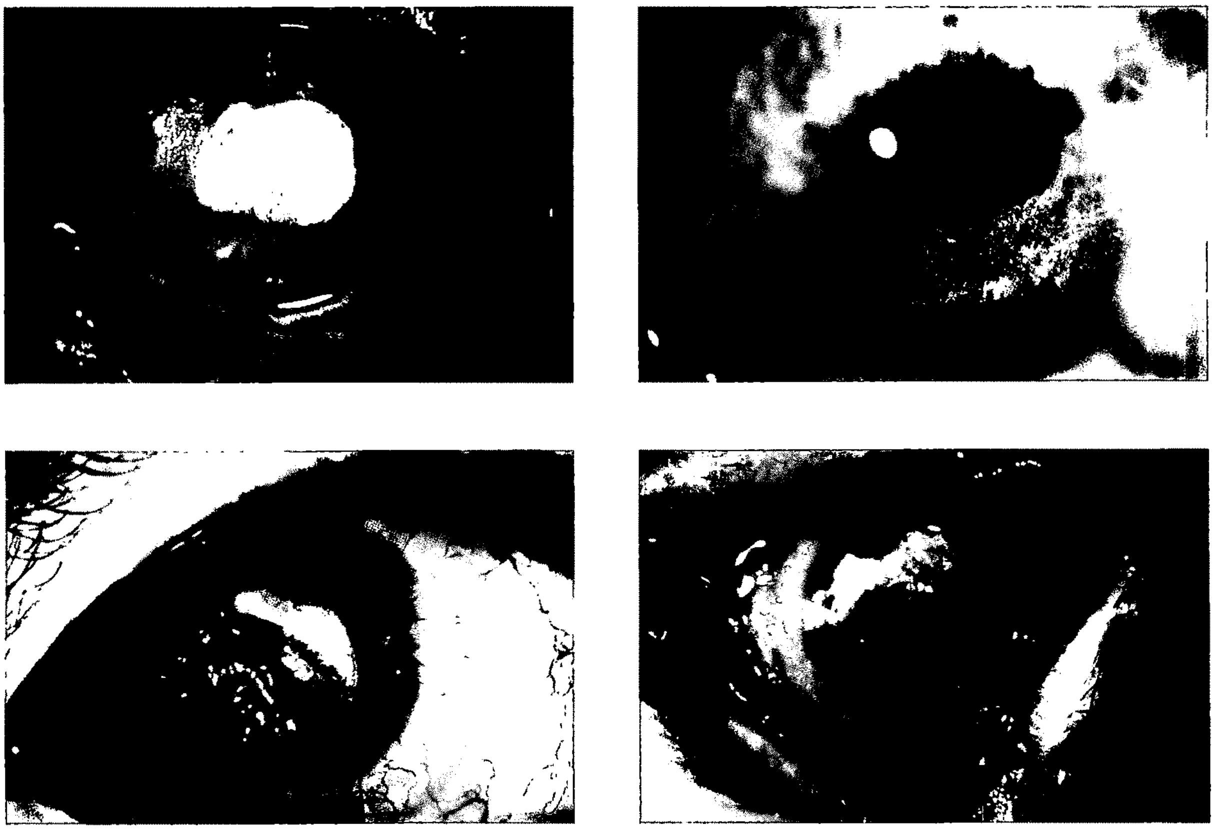

Figure (Leibowitz). Appearance of ciprofloxacin precipitate on corneal surface.

chance of adverse reactions with the use of multiple, fortified medications. Subconjunctival antibiotic injections can cause adverse reactions characterized by pain, discomfort, mydriasis, corneal endothelial changes, corneal edema, corneal opacities, conjunctival sloughing/necrosis, and subconjunctival hemorrhage.[7,8] Inadvertent perforation of the globe can occur with concomitant intraretinal hemorrhage, macular infarction, and other forms of retinal toxicity, which results in permanent reduction or loss of vision.[7,8] Moreover, the organisms commonly associated with bacterial corneal ulcers are increasingly resistant to standard therapy[9]; Borrmann and Leopold[10] reported 8% to 10% of the ulcerative keratitis caused by *P. aeruginosa* are resistant to aminoglycoside therapy, and it appears that resistance by gram-positive organisms also is increasing.

The in vitro activity for ciprofloxacin as well as for gentamicin and tobramycin is shown in Table 15. These in vitro data indicate that ciprofloxacin is highly effective against the more common ocular pathogens associated with corneal ulcers and demonstrate that its degree of effectiveness and spectrum of action are greater than the two aminoglycosides. This observation, in turn, suggests that ciprofloxacin might effectively be used as a single agent to treat bacterial keratitis.

Results of the clinical study reported here support this therapeutic approach. Evaluation by the treating ophthalmologist demonstrated that ciprofloxacin was effective for treatment of bacterial corneal ulcers. Symptoms and signs resolved or improved during the course of treatment with ciprofloxacin, and clinically successful outcomes were obtained. Slightly better than a 90% success rate was obtained among all patients with bacterial keratitis treated only with topical ciprofloxacin 0.3% for whom the data necessary for evaluation were available. Comparing these results against two different sets of controls, including concurrent treatment with at least two fortified antibiotics, ciprofloxacin appears equal in its ability to eradicate

TABLE 15
RELATIVE IN VITRO SENSITIVITIES OF COMMON BACTERIAL CORNEAL PATHOGENS*

	MIC (μG/ML)		
BACTERIA	CIPROFLOXACIN	TOBRAMYCIN	GENTAMICIN
St. aureus	0.5	6.3	12.5
S. epidermidis	0.5	3.1	12.5
Other coagulase-negative staphylococci	0.5	6.3	6.0
St. pneumoniae	2.0	12	50
Streptococcus Groups A, C, and D	2.0	>30	>30
Neisseria sp.	<0.06	>6	>4.0
H. influenza	<0.06	4	1.0
P. aeruginosa	<1.0	6.3	8.0

*Compiled from published data.

bacterial infections of the cornea. At present, ciprofloxacin is the only ophthalmic antibiotic that has been shown in a large clinical study to be highly effective at its commercially available concentration as initial therapy for bacterial keratitis.

Systemic absorption of ciprofloxacin ophthalmic solution is negligible. Plasma levels of ciprofloxacin, drawn within 30 minutes after drug administration at several points during a seven-day topical dosing schedule for the treatment of conjunctivitis[11] and during the first seven days of the dosing schedule described in the present study, ranged from nonquantifiable to mean peak levels of 4.7 ng/ml. The chemical assay was able to detect < 1.25 ng/ml. For comparison, the mean peak ciprofloxacin plasma level obtained after topical dosing is approximately 450-fold less than that seen after a single oral dose of 250 mg ciprofloxacin,[12] indicating a wide margin of safety for topically administered ophthalmic ciprofloxacin. No abnormal renal, liver, blood, protein, lipid, electrolyte, bone, or urine laboratory values have been reported resulting from the topical use of ophthalmic ciprofloxacin.[12]

Ciprofloxacin ophthalmic solution 0.3% was evaluated for safety in more than 1,500 patients, including healthy volunteers, patients with bacterial keratitis, and patients with blepharitis, conjunctivitis, and blepharoconjunctivitis. No serious events related, or possibly related, to ciprofloxacin occurred. Nonserious ocular events generally were reversible with continued ciprofloxacin treatment. Nonocular untoward events related, or possibly related, to therapy were rare and primarily were limited to reports of transient taste abnormality. Among those examined for safety of ciprofloxacin therapy, only ten (1.0%) patients discontinued treatment because of treatment-related, or possibly related, untoward events. These clinical data support the conclusion that ciprofloxacin ophthalmic solution 0.3% lacks ophthalmic and systemic toxicity and is well tolerated by patients in multiple dosing regimens.

A potential limitation for routine use of this agent is the possibility for the development of resistance to the drug. However, the mechanism of development of resistance to ciprofloxacin is that of chromosomal mutation, rather than plasmid acquisition.[13] Thus, in contrast to other antibacterials, resistance, to ciprofloxacin occurs at a low frequency, segregates independently from other types of antibacterial resistance, and is not spread to other organisms through mobile resistance factors or plasmids.

The data generated in this multicenter clinical study demonstrate that, both clinically and microbiologically, ciprofloxacin is safe and effective as a single agent for the treatment of bacterial corneal ulcers. It renders treatment easier than the currently recommended approach and has the potential for reducing morbidity and increasing compliance.

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References

1. Wolfson, J. S., and Hooper, D. C.: Fluoroquinolone antimicrobial agents. Clin. Antimicrobiol. Rev. 2:378, 1989.
2. Eliopoulos, G. M., and Eliopoulos, C. T.: Quinolone antimicrobial agents. Activity in vitro. In Wolfson, J. S., and Hooper, D. C. (eds.): Quinolone Antimicrobial Agents. Washington, D.C., American Society for Microbiology, 1989, pp. 35–70.
3. Asbell, P., and Stenson, S.: Ulcerative keratitis. Survey of 30 years' laboratory experience. Arch. Ophthalmol. 100:77, 1982.
4. Liesegang, T. J., and Forster, R. F.: Spectrum of microbial keratitis in south Florida. Am. J. Ophthalmol. 90:38, 1980.
5. Coster, D. J., Wilhelmus, K., Peacock, J., and Jones, B. R.: Suppurative keratitis in London. In Trevor-Roper, T. (ed.): European Society of Ophthalmology. The Cornea in Health and Disease. London, Academic Press, 1981, p. 395.
6. Jones, D. B.: Early diagnosis and therapy of bacterial corneal ulcers. Int. Ophthalmol. Clin. 13:1, 1973.
7. Leibowitz, H. M.: Bacterial keratitis. In Corneal Disorders. Clinical Diagnosis and Management. Philadelphia, W. B. Saunders Co., 1984, pp. 353–386.
8. Liesegang, T. J.: Bacterial and fungal keratitis. In Kaufman, H. E., Barron, B. A., McDonald, M. B., and Waltman, S. R. (eds.): The Cornea. New York, Churchill Livingstone, 1988, pp. 217–248.
9. Mehta, N. J., Webb, R. M., and Krohel, G. B.: Clinical inefficiency of tobramycin and gentamicin sulfate in the treatment of ocular infections. Cornea 3:228, 1984.
10. Borrmann, L. R., and Leopold, I. H.: The potential use of quinolones in future ocular antimicrobial therapy. Am. J. Ophthalmol. 106:227, 1988.
11. Leibowitz, H. M.: Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. Am. J. Ophthalmol. 112(suppl):29S, 1991.
12. Hawkins, V., Schneiweiss, F., and Mayer, P. R.: Plasma concentrations of ciprofloxacin in normal volunteers following topical ocular administration. Alcon Clinical Monitor's Report 064:38610:1289.
13. Neu, H. C.: Bacterial resistance to quinolones. Rev. Infect. Dis. 10(Suppl 1):57, 1988.
14. Campoli-Richards, D. M., Monk, J., Price, A., Benfield, P., Todd, P. A., and Ward, A.: Ciprofloxacin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 35:373, 1988.
15. Atkinson, B.: Species incidence and minimum inhibitory concentration. In Lorian, V. (ed.): Antibiotics in Laboratory Medicine. Baltimore, Williams & Wilkins Co., 1980, pp. 607–713.
16. Eickhoff, T., and Ehret J.: In vitro activity of netilmycin compared with gentamicin, tobramycin, amikacin and kanamycin. Antimicrob. Agents Chemother. 11:791, 1977.
17. Waitz, J., Moss Jr., E., Drube, C., and Weinstein, M.: Comparative activity of sisomicin, gentamicin, kanamycin and tobramycin. Antimicrob. Agents Chemother. 6:431, 1972.

Conclusion

In the early 1970s, Dan B. Jones, M.D., published recommendations for a standardized procedural approach to the diagnosis and treatment of bacterial keratitis.[1,2] With modifications, these recommendations continue to serve as the standard of care, and form the basis for authoritative discussions of the evaluation and treatment of this potentially devastating condition. Therapy relies principally on the topical administration of fortified antibiotics (that is, ophthalmic formulations at substantially higher concentrations than those commercially available and high concentration formulations of drugs not commercially available for ophthalmic use). These must be individually prepared by the ophthalmologist or the pharmacist for each patient. Because any bacterial organism can produce keratitis if conditions are optimal, at least two fortified topically administered antibiotics are used in the initial therapeutic regimen to achieve broad antibacterial coverage.

Although cumbersome, this regimen has withstood the test of time and has proven to be highly effective. Data presented in this monograph strongly suggest that topical therapy with ciprofloxacin 0.3% eradicates bacterial keratitis as effectively as conventional treatment with a minimum of two fortified antibiotics. Has the ophthalmologist's long awaited dream, that of the availability of a single, commercially available ophthalmic antibiotic suitable for initial treatment of all cases of bacterial keratitis, come true? Perhaps, but extreme caution is in order. First, one must not forget that complete antibacterial coverage is not achieved by either initial conventional or ciprofloxacin therapy. Second, although many investigators participated and many cases were evaluated, the data we report represent only the results of a single study. Independent confirmation is required before we can safely assume that we have truly arrived at a new era in the treatment of bacterial keratitis. However, these data are sufficiently convincing and provocative to encourage further studies without delay, and to induce cautious optimism of a major breakthrough.

HOWARD M. LEIBOWITZ, M.D.

References

1. Jones, D. B.: Early diagnosis and therapy of bacterial corneal ulcers. Int. Ophthalmol. Clin. 13:1, 1973.

2. ———: A plan for antimicrobial therapy in bacterial keratitis. Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:OP95, 1975.

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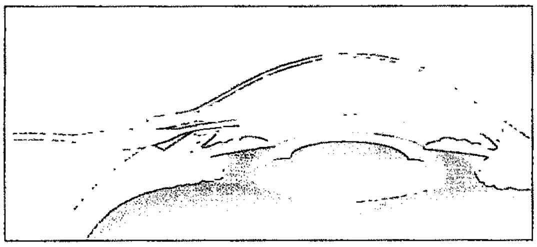

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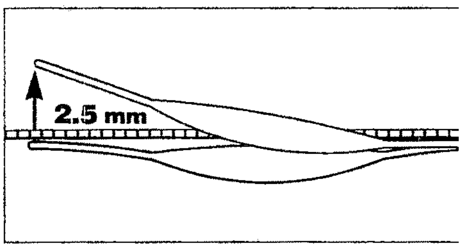

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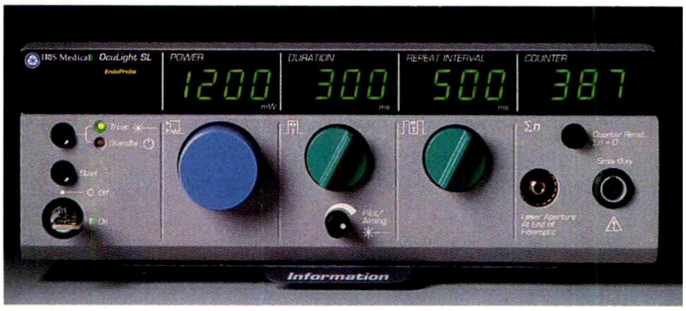

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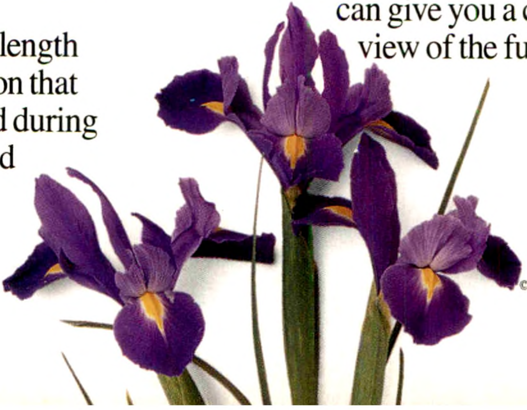

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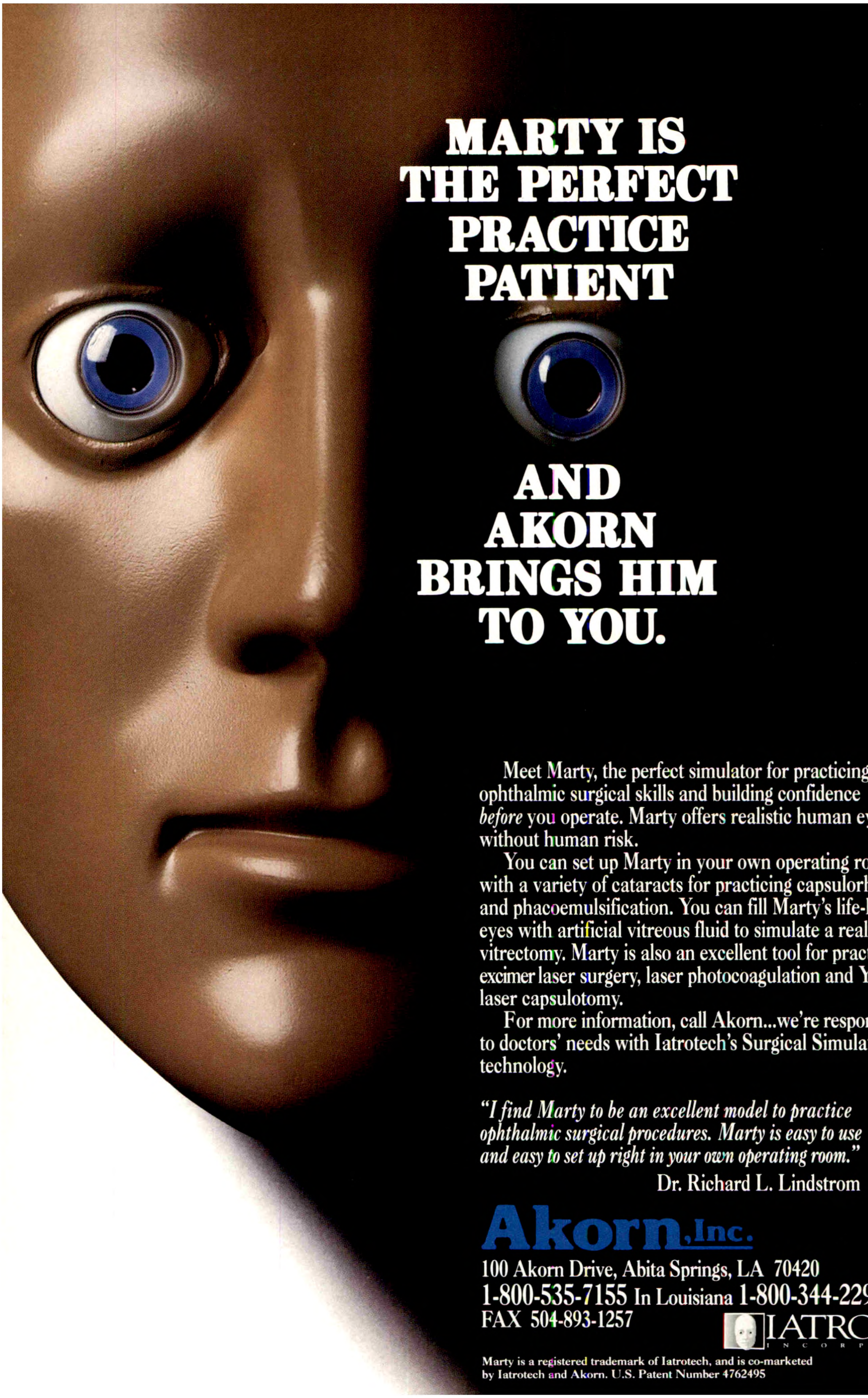
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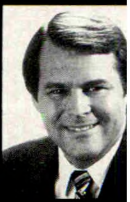

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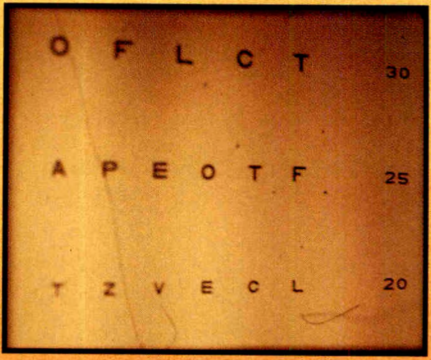

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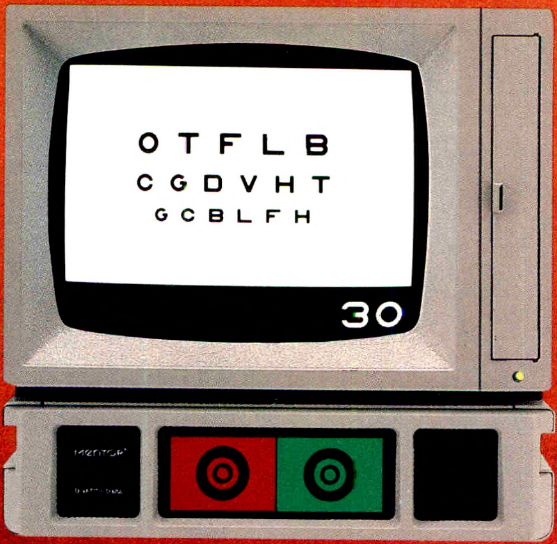

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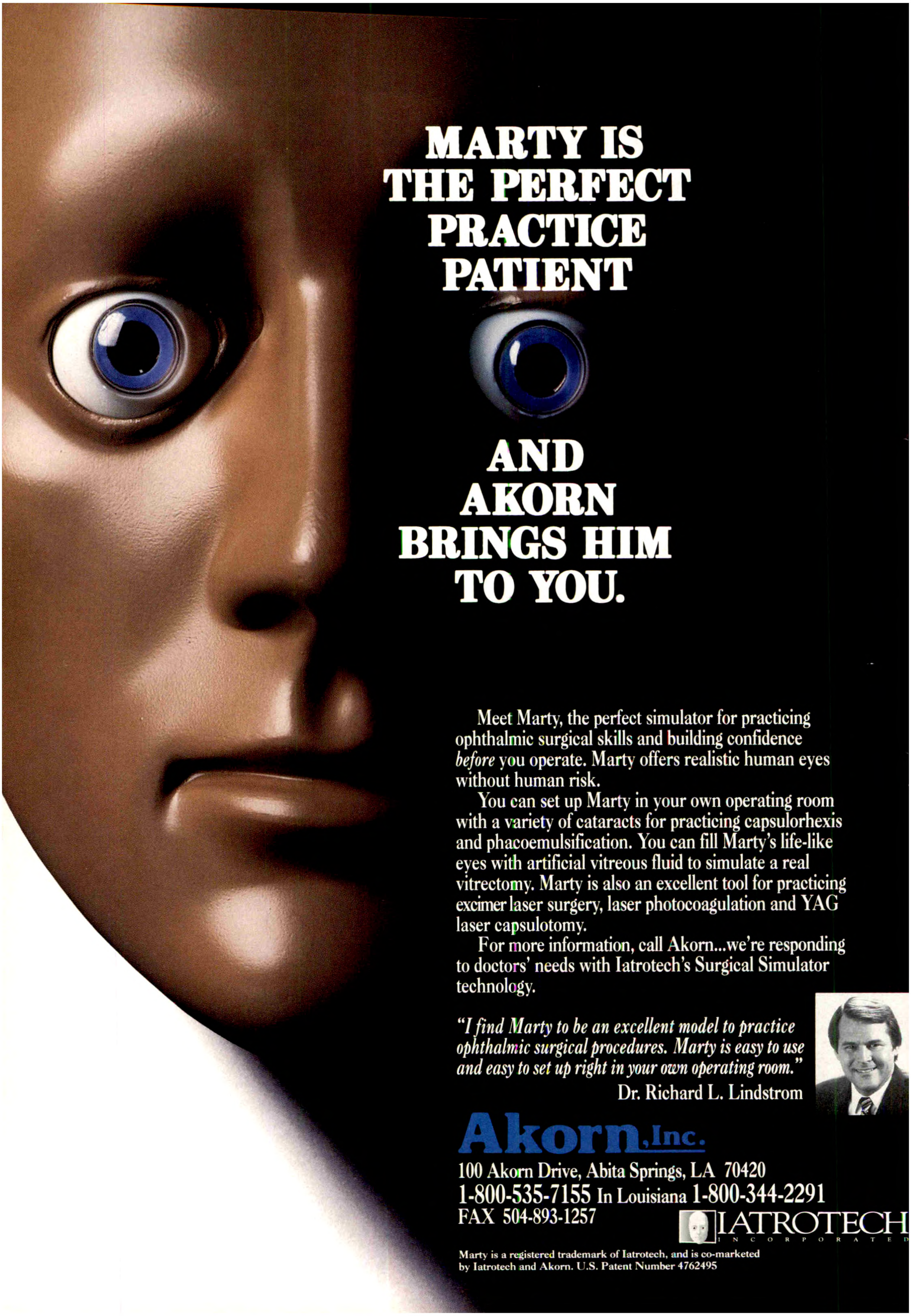
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Retinal Toxicity in Human Immunodeficiency Virus–infected Children Treated With 2′,3′-Dideoxyinosine

Scott M. Whitcup, M.D., Karina M. Butler, M.B., Rafael Caruso, M.D.,
Marc D. de Smet, M.D., Benjamin Rubin, M.D., Robert N. Husson, M.D.,
Juan S. Lopez, M.D., Rubens Belfort, Jr., M.D., Philip A. Pizzo, M.D.,
and Robert B. Nussenblatt, M.D.

To assess the safety and antiretroviral activity of 2′,3′-dideoxyinosine, we enrolled 43 children with symptomatic (Centers for Disease Control class P-2) human immunodeficiency virus infection in a Phase I-II study and monitored them prospectively for the development of ocular complications secondary to HIV infection or drug toxicity. Follow-up ranged from 12 to 103 weeks with a median follow-up of 71 weeks. Three of 43 children (7.0%) developed peripheral atrophy of the retinal pigment epithelium during treatment with 2′,3′-dideoxyinosine. The two children with the most severe retinal atrophy were enrolled in the study at the highest dosage studied (540 mg/m²/day). In contrast to findings in children, no retinal atrophy in HIV-infected adults treated with 2′,3′-dideoxyinosine has been evident to date.

Ocular complications in human immunodeficiency virus–infected patients result from several causes including opportunistic infections, retinal vasculopathy, malignancy, and drug-related toxicity. Currently, some patients with the acquired immunodeficiency syndrome are treated with 2′,3′-dideoxyinosine, a purine analogue with antiretroviral activity. Although ocular disease is reported in as many as 75% of HIV-infected adults,[5] ocular complications may develop less frequently in HIV-infected children. The purine nucleoside analogue 2′,3′-dideoxyinosine has in vitro activity against HIV in both T cells and monocytes.[6,7] Several clinical trials have examined the efficacy and safety of 2′,3′-dideoxyinosine in treating HIV-infected patients. Dose-limiting side effects have included painful peripheral neuropathy and pancreatitis. One case of optic neuritis associated with 2′,3′-dideoxyinosine has been reported[8]; however, to date, no marked retinal toxicity has been associated with 2′,3′-dideoxyinosine treatment. We studied evidence suggesting that higher doses of 2′,3′-dideoxyinosine may result in retinal atrophy in some HIV-infected children.

Subjects and Methods

Forty-three class P-2 symptomatic HIV-infected children (27 previously untreated children and 16 children previously treated with zidovudine) were enrolled in a prospective, Phase I-II study to assess the safety and antiretroviral activity of 2′,3′-dideoxyinosine at doses of 60, 120, 360, and 540 mg/m² given orally in three divided doses daily. Details of the study and results of the 24-week follow-up were reported previously.[9] Children were monitored prospectively for the development of ocular disease. Children underwent an ocular examination before treatment that included assessment of visual acuity, examination of the anterior segment of the eyes, and ophthalmoscopy through a dilated pupil. Repeat eye examinations were then performed at three- to six-month intervals. Electrophysiologic studies were also performed on two of the three children who developed retinal atrophy.

Accepted for publication Sept. 18, 1991.

From the Laboratory of Immunology (Drs. Whitcup, de Smet, Rubin, Lopez, Belfort, Nussenblatt, and Butler) and Ophthalmic Genetics and Clinical Services (Dr. Caruso), National Eye Institute; and the Pediatric Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland (Drs. Husson and Pizzo).

Reprint requests to Scott M. Whitcup, M.D., Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bldg. 10, Rm. 10N202, Bethesda, MD 20892.

Results

From Jan. 1, 1989, through Jan. 1, 1991, 43 children with symptomatic HIV infection (27 previously untreated and 18 with refractory disease or intolerance to zidovudine) were enrolled in the study and monitored for ocular complications. Follow-up ranged from 12 to 103 weeks, with a median follow-up of 71 weeks. During the two-year period, eight children died and 12 children were withdrawn because of progressive disease or toxicity. Three of 43 children (7.0%) with symptomatic (Centers for Disease Control class P-2) HIV infection developed well-circumscribed, atrophic retinal lesions during treatment with 2′,3′-dideoxyinosine (Figs. 1 through 3). The clinical characteristics of the three children who developed retinal toxicity were analyzed (Table). All three children had normal results of eye examinations before treatment with 2′,3′-dideoxyinosine was started, with the exception of peripheral bands of vitreous condensation in both eyes of Patient 3. No family history of retinal diseases was found in any of the children, and examination of the parents disclosed no retinal lesions. Treatment with 2′,3′-dideoxyinosine was discontinued in Patients 1 and 2 because of progressive retinal atrophy. Both of these children are currently being treated with zidovudine. Patient 3 is being monitored closely for clinical signs of progressive retinal atrophy. Visual acuity has remained 20/20 in all three patients. Although difficult to assess in children, some constriction of the visual field to the V_{4e} stimulus was observed with Goldmann perimetry in Patient 1.

Two of the three children with retinal lesions were among the ten patients enrolled at the highest dosage studied (540 mg/m^2/day). These two children developed the most severe retinal atrophy, which led to the discontinuation of treatment with 2′,3′-dideoxyinosine. The third patient, enrolled at a dosage of 120 mg/m^2/day that was later increased to 360 mg/m^2/day, also developed retinal atrophic lesions. Seven of the ten patients enrolled at a 2′,3′-dideoxyinosine dosage of 540 mg/m^2/day and 26 of 33 patients enrolled at lower dosages were treated with 2′,3′-dideoxyinosine for at least 36 weeks, the earliest time that retinal lesions have been observed. One patient, originally enrolled at the 360-mg/m^2/day dosage, had his dosage of 2′,3′-dideoxyinosine briefly increased to 540 mg/m^2/day after 37 weeks of treatment.

Serum levels of p24 antigen decreased in two of the three children during treatment with 2′,3′-dideoxyinosine, and serum CD4 counts increased in one of the three children during treatment. None of the children had evidence of cytomegalovirus retinitis before treatment with 2′,3′-dideoxyinosine. One patient developed cytomegalovirus retinitis three months after starting treatment with 2′,3′-dideoxy-

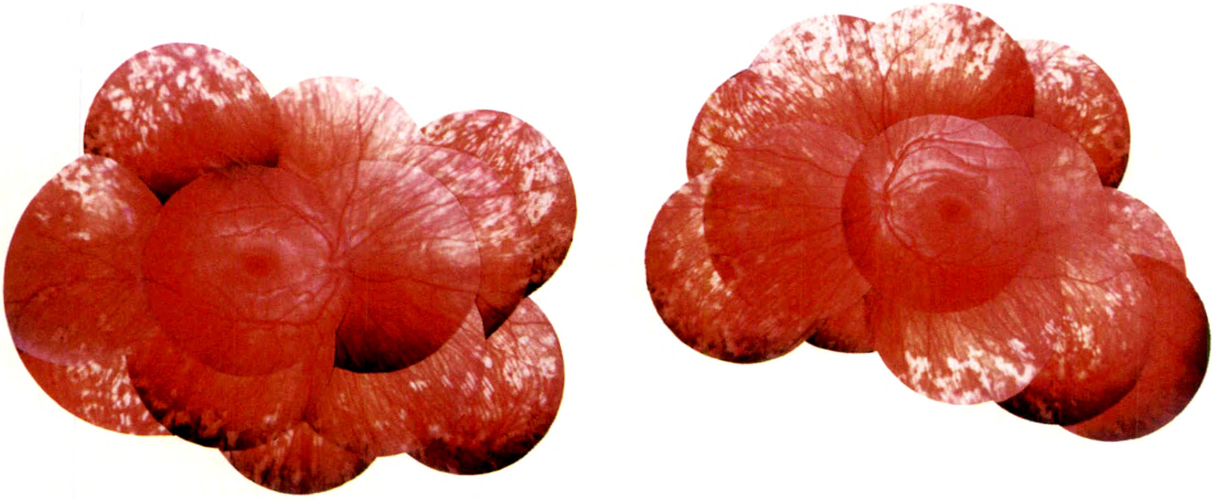

Fig. 1 (Whitcup and associates). Patient 1. Left, A montage of fundus photographs of the right eye shows extensive, midperipheral retinal atrophy predominantly involving the retinal pigment epithelium. Retinal lesions were well circumscribed with some hyperpigmentation at the borders of the lesions. Right, A montage of fundus photographs of the left eye.

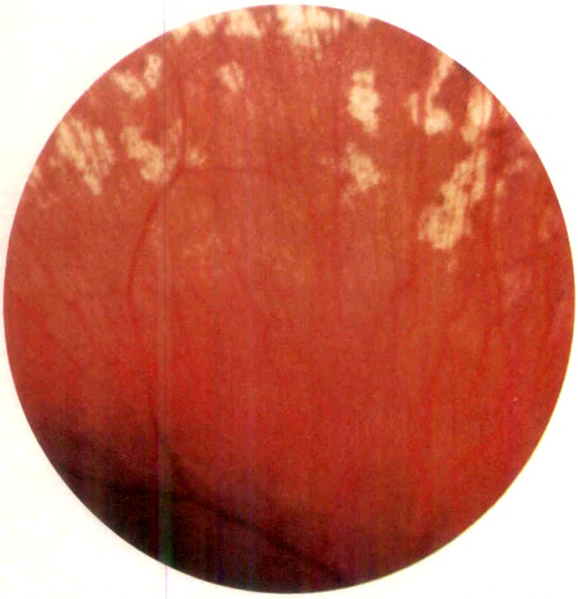

Fig. 2 (Whitcup and associates). Patient 2. Fundus photograph of retinal lesions in the right eye.

inosine, but to date, no other patient has developed cytomegalovirus retinitis.

Serial electroretinography was performed in Patient 1 and demonstrated a diminution in the maximal retinal response during treatment with 2′,3′-dideoxyinosine (Fig. 4). Electro-oculography was performed on Patients 1 and 3. Electro-oculograms were considered normal if the Arden ratio of the light-adapted peak to the dark-adapted trough was greater than 2.0 (normal mean ± 2 standard deviations).[10] Electro-oculograms were considered to be probably abnormal if the Arden ratio fell between 1.75 and 2.0, and definitely abnormal if the Arden ratio was less than 1.75. The electro-oculogram was abnormal in both eyes of Patient 1, with an Arden ratio 1.43 in the right eye and 1.78 in the left eye (Fig. 5, left). The electro-oculogram was normal in Patient 3, with an Arden ratio of 2.09 in the right eye and 2.46 in the left eye. Patient 2 was too young to undergo electrophysiologic testing.

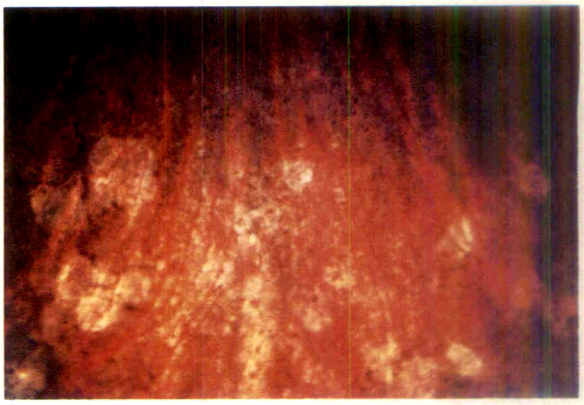

Fig. 3 (Whitcup and associates). Patient 3. Fundus photograph of retinal lesions in the right eye.

Two of the three patients who developed retinal atrophy were treated with 2′,3′-dideoxyinosine at 540 mg/m^2/day for 34 and 32 weeks, respectively. Retinal atrophy progressed in these two patients, even after the dosage of 2′,3′-dideoxyinosine was decreased to 360 mg/m^2/day. No progression of the retinal atrophy was seen after treatment with 2′,3′-dideoxyinosine was discontinued in these two patients, and results of electro-oculography returned to normal three months after treatment with 2′,3′-dideoxyinosine was stopped in Patient 1 (Fig. 5, right).

Discussion

We found evidence of retinal atrophy in three of 43 children treated with 2′,3′-dideoxyinosine for symptomatic HIV infection. The retinal lesions in the three children predominantly involved the retinal pigment epithelium. Ocu-

TABLE

CHARACTERISTICS OF PATIENTS WITH 2′, 3′-DIDEOXYINOSINE-ASSOCIATED RETINAL LESIONS

PATIENT NO., AGE (YRS), GENDER	MAXIMAL DOSE OF 2′, 3′-DIDEOXYINOSINE (MG/M^2/DAY)	WEEKS AT MAXIMAL DOSE	TOTAL DOSE OF 2′, 3′-DIDEOXYINOSINE WHEN RETINAL LESIONS NOTED (G/M^2)	WEEKS OF TREATMENT WITH 2′, 3′-DIDEOXYINOSINE WHEN RETINAL LESIONS NOTED
1, 7, F	540	36	159.0	46
2, 2, F	540	32	189.6	36
3, 8, M	360	58	189.5	82

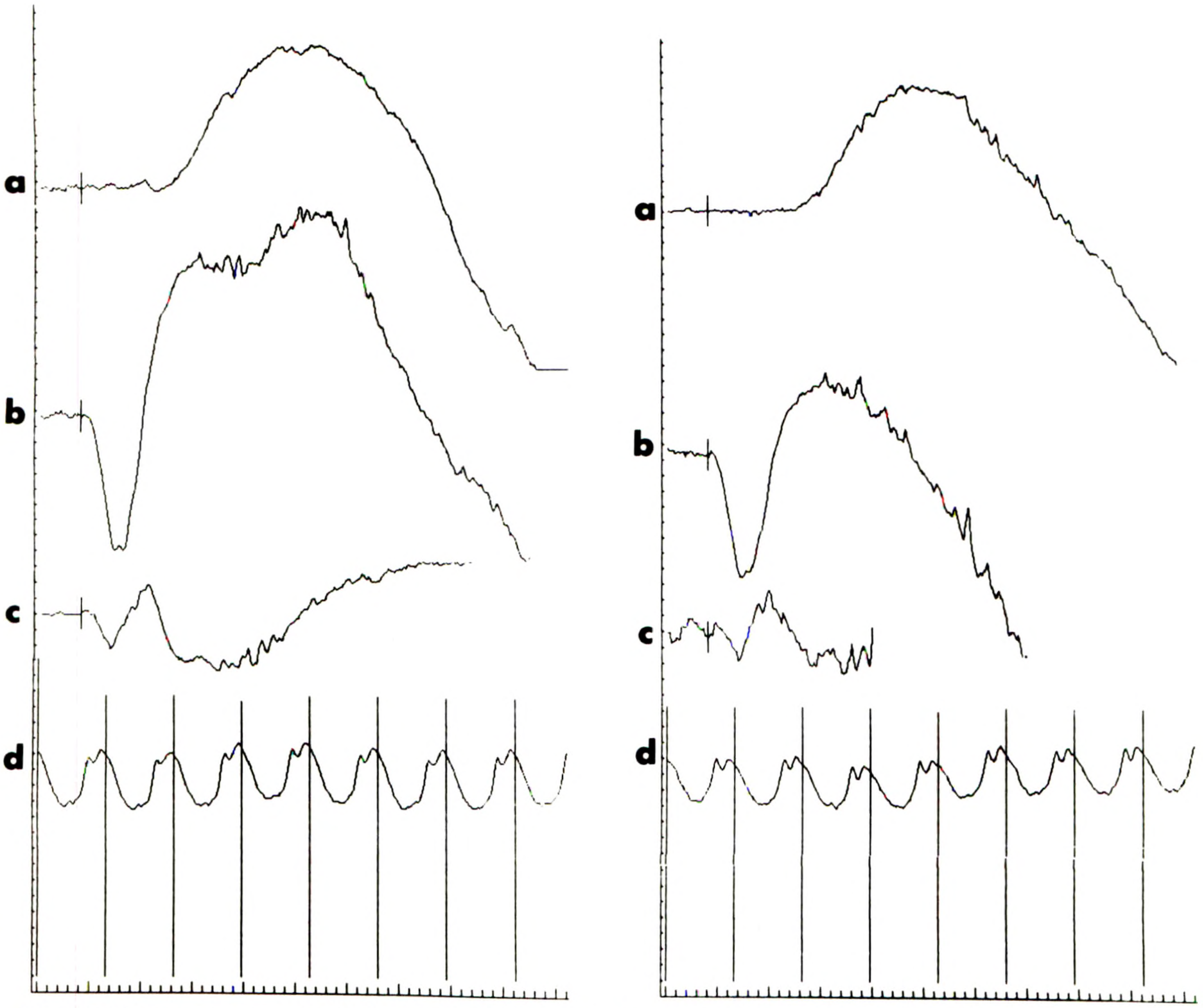

Fig. 4 (Whitcup and associates). Patient 1. Electroretinograms of the right eye. From uppermost to lowermost, the waveforms correspond to the rod-mediated response (a), the maximal retinal response (b), the cone-mediated response (c), and the flicker response (d). Left, Electroretinogram shows that the cone-mediated response was in the lower normal range. All other responses were normal. Right, Repeat electroretinogram two months later shows a reduction in the maximal retinal response. The other responses were unchanged.

lar abnormalities in adults treated with 2′,3′-dideoxyinosine have not been well studied in clinical studies to date; however, eye examinations were not performed as part of the routine examination in those studies.

Retinal toxicity affecting the retinal pigment epithelium has been reported with other drugs such as thioridazine and NP-207, a related phenothiazine preparation.[11-15] Additionally, Cunningham, Friedberg, and Carr[16] reported a case of presumed clofazamine-induced bull's-eye maculopathy and generalized retinal degeneration in a patient with AIDS, and suggested that patients with AIDS may be particularly susceptible to drug-related retinal toxicity.

Retinal lesions were observed as early as 36 weeks after treatment with 2′,3′-dideoxyinosine was initiated. Importantly, progression of retinal atrophy continued even at lower doses of 2′,3′-dideoxyinosine, but ceased after treatment was discontinued. Because retinal lesions are located in the midperiphery of the fundus, they could easily be missed on examination with direct ophthalmoscopy alone, especially through an undilated pupil. We are currently monitoring all children being treated with 2′,3′-dideoxyinosine with dilated fundus examinations by indirect ophthalmoscopy every three to six months to check for development of atrophic lesions. If retinal lesions are

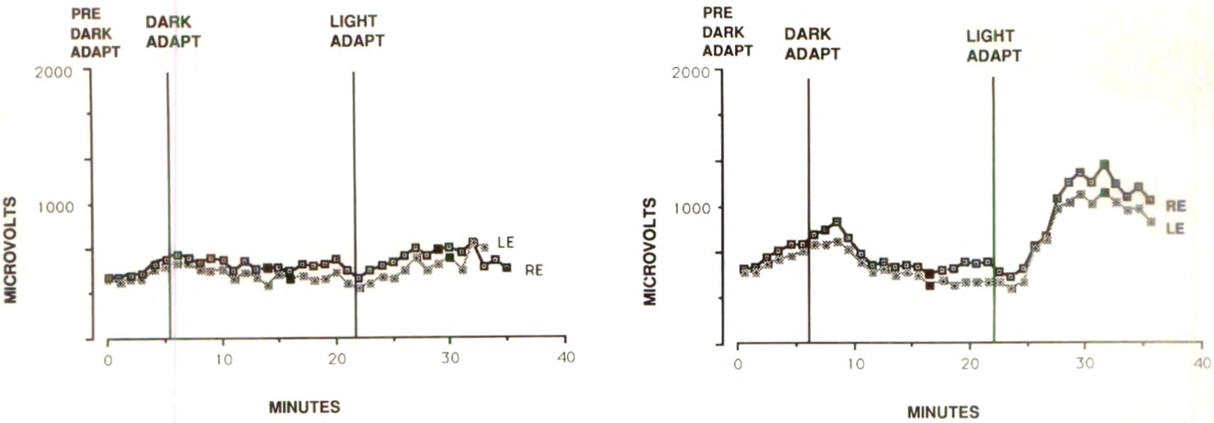

Fig. 5 (Whitcup and associates). Patient 1. Left, Electro-oculogram obtained during 2′, 3′- dideoxyinosine treatment. Solid boxes indicate the dark-adapted trough and light-adapted peak for each eye. The ratio of the light-adapted peak to the dark-adapted trough (Arden ratio) of the right eye was 1.37 and the Arden ratio of the left eye was 1.78. Right, Electro-oculogram 12 weeks after the discontinuation of dideoxyinosine treatment was normal. The Arden ratio of the right eye was 2.79 and the Arden ratio of the left eye was 2.85.

observed, children should be initially reexamined monthly to assess progression. Because these lesions appear to occur initially in the midperiphery of the fundus, central vision is not immediately threatened, but slight constriction of the peripheral visual field was observed in one child who could be tested reliably. A decision to discontinue treatment with 2′,3′-dideoxyinosine would depend on the clinical situation; however, if the lesions progress notably, cessation of 2′,3′-dideoxyinosine treatment may be warranted. The role of electrophysiologic testing in screening and monitoring patients with possible 2′,3′-dideoxyinosine toxicity remains to be determined.

Nevertheless, electroretinography and electro-oculography provided valuable information about the retinal atrophy in these patients. Patient 1 had electroretinography and electro-oculography each performed twice. Electroretinography, which is a record of the electrical response generated by neural and nonneuronal cells in the retina, showed diminished cone-mediated responses that worsened during treatment with 2′,3′-dideoxyinosine, suggesting involvement of these photoreceptors. Electro-oculography, in part, measures the function of the retinal pigment epithelium[17] and was therefore used to test children with suspected 2′,3′-dideoxyinosine toxicity because the retinal lesions appeared to affect predominantly the retinal pigment epithelium. The electro-oculogram was abnormal in one of the two patients with retinal atrophy who were tested. The electrophysiologic and ophthalmoscopic findings suggested a diffuse dysfunction of the retinal pigment epithelium. It would have been desirable to perform more extensive electrophysiologic tests including electroretinography, electro-oculography, visual fields, dark adaptation, and color vision testing on all the patients examined, but testing was limited to those children able to tolerate the test.

Electro-oculography has been useful in monitoring several drug-related retinal toxicities such as chloroquine retinopathy, in which the drug is concentrated in the retinal pigment epithelium.[16] The finding of a normal electroretinogram in the presence of an abnormal electro-oculogram is suggestive of a toxic retinopathy affecting the retinal pigment epithelium,[18] and these electrophysiologic studies may be useful in monitoring the progression of retinal toxicity in patients with retinal atrophy associated with 2′,3′-dideoxyinosine. Nevertheless, it is not known if electro-oculography is a more sensitive indicator of toxic retinopathy associated with 2′,3′-dideoxyinosine treatment than is clinical examination. Gouras and Gunkel[19] stated that the electro-oculography was not a sensitive indicator of mild degrees of chloroquine retinopathy, particularly in patients no longer being treated with the drug.

The atrophic retinal lesions progressed in two of the three patients with continued treatment with 2′,3′-dideoxyinosine, even after the dose was decreased. Fortunately, no progression has been observed in the two patients with retinal atrophy in whom the treatment with the drug has been stopped. Furthermore, the electro-oculogram has returned to normal in Patient 1 after treatment with 2′,3′-dideoxyinosine was discontinued, suggesting that some of the retinal toxicity is reversible. Her constricted visual field has remained constant, however, and probably indicates some permanent damage to the photoreceptors.

The development of retinal atrophy during treatment with 2′,3′-dideoxyinosine, and lack of progression after 2′,3′-dideoxyinosine treatment was discontinued in two patients, suggest a causal relationship. This relationship is further supported by the return of normal electro-oculographic recordings after 2′,3′-dideoxyinosine treatment was stopped. We have not seen peripheral retinal atrophy in over 100 pediatric patients with AIDS before starting treatment with 2′,3′-dideoxyinosine, including children treated with zidovudine or with zidovudine alternating with dideoxycytidine.[20] Although Patient 1 had a probable episode of herpes zoster infection involving the central nervous system, and was also treated with zidovudine, no fundus lesions were observed before starting treatment with 2′,3′-dideoxyinosine. Patient 2 also developed prominent and progressive retinal atrophy during 2′,3′-dideoxyinosine treatment. Patient 3 has developed early clinical signs of retinal atrophy that are worse in the right eye than in the left, despite treatment with moderate doses and an intermediate cumulative dose of 2′,3′-dideoxyinosine. His electro-oculogram has remained normal, although the Arden ratio is at the lower limit of normal in the right eye. We are also monitoring this patient closely for evidence of further retinal atrophy or diminution in the electro-oculogram.

Higher doses of 2′,3′-dideoxyinosine appear to be associated with retinal atrophy in some HIV-infected children, which manifests as lesions predominantly involving the retinal pigment epithelium. Retinal atrophy was found in two of ten patients enrolled in the study at the highest dosage of 2′,3′-dideoxyinosine studied (540 mg/m^2/day), and in one patient enrolled at 120 mg/m^2/day who was later treated with 360 mg/m^2/day for over one year. The most extensive retinal atrophy was associated with doses of 2′,3′-dideoxyinosine that were higher than the dose usually used in clinical practice. In contrast to findings in children, we found no evidence of retinal atrophy to date in adults treated with 2′,3′-dideoxyinosine, even in patients treated with the drug for over two years at dosages greater than 2,000 mg/m^2/day for a period of four to six weeks. Additionally, electro-oculograms have been normal in all the adult patients tested. Nevertheless, close monitoring of all patients treated with 2′,3′-dideoxyinosine for the development of retinal atrophy seems warranted.

References

1. Mitsuya, H., Jarrett, R. F., Matsukura, M., Di Marzo Veronese, F., DeVico, A. L., Sarngadharan, M. G., Johns, D. G., Reitz, M. S., and Broder, S.: Long-term inhibition of human T-lymphotropic virus type III/lymphadenopathy-associated virus (human immunodeficiency virus) DNA synthesis and RNA expression in T cells protected by 2′,3′-dideoxynucleosides in vitro. Proc. Natl. Acad. Sci. U.S.A. 84:2033, 1987.

2. Bhalla, K., Birkhofer, M., Rarick, M., and Gill, P.: Modulation of the growth inhibitory effects of 2′,3′-dideoxyadenosine on human myeloid progenitor cells by rGM-CSF and coformycin. Proc. Am. Assoc. Cancer Res. 30:569, 1989.

3. Yarchoan, R., Mitsuya, H., Thomas, R. V., Pluda, J. M., Hartman, N. R., Perno, C. F., Marczyk, K. S., Allain, J. P., Johns, D. G., and Broder, S.: In vivo activity against HIV and favorable toxicity profile of 2′,3′-dideoxyinosine. Science 245:412, 1989.

4. Fauci, A. S.: ddI. A good start, but still phase I. N. Engl. J. Med. 322:1386, 1990.

5. Mines, J. A., and Kaplan, H. J.: Acquired immunodeficiency syndrome (AIDS). The disease and its ocular manifestations. Int. Ophthalmol. Clin. 28:73, 1986.

6. Mitsuya, H., and Broder, S.: Strategies for antiviral therapy in AIDS. Nature 325:773, 1987.

7. Perno, C. F., Yarchoan, R., Cooney, D. A., Hartman, N. R., Webb, D. S. A., Hao, Z., Mitsuya, H., Johns, D. G., and Broder, S.: Replication of human immunodeficiency virus in monocytes. Granulocyte/macrophage colony-stimulating factor (GM-CSF) potentiates viral production yet enhances the antiviral effect mediated by 3′-azido-2′3′-dideoxythymidine (AZT) and other dideoxynucleoside congeners of thymidine. J. Exp. Med. 169:933, 1989.

8. Lafeuillade, A., Aubert, L., Chaffanjon, P., and Quilichini, R.: Optic neuritis associated with dideoxyinosine. Lancet 337:615, 1991.

9. Butler, K. M., Husson, R. N., Balis, F. M., Brouwers, P., Eddy, J., El-Amin, D., Gress, J., Hawkins, M., Jarosinski, P., Moss, H., Poplack, D., Santacroce, S., Venzon, D., Wiener, L., Wolters, P., and Pizzo, P. A.: Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. N. Engl. J. Med. 324:137, 1991.

10. Krill, A. E.: Electrooculogram. In Krill, A. E. (ed.): Hereditary Retinal and Choroidal Diseases. New York, Harper and Row, 1972, pp. 277–295.

11. Meredith, T. A., Aaberg, T. M., and Willerson, W. D.: Progressive chorioretinopathy after receiving thioridazine. Arch. Ophthalmol. 96:1172, 1978.

12. Fishman, G. A.: Thioridazine hydrochloride (Mellaril) toxic pigmentary chorioretinopathy. In Smith, J. L. (ed.): Neuro-ophthalmology Focus. New York, Masson Publishers, 1982, pp. 109–118.

13. Davidorf, F. H.: Thioridazine pigmentary retinopathy. Arch. Ophthalmol. 90:251, 1973.

14. Goar, E. L., and Fletcher, M. C.: Toxic chorioretinopathy following the use of NP-207. Am. J. Ophthalmol. 44:603, 1957.

15. Arden, G. B., and Fojas, M. R.: Electrophysiological abnormalities in pigmentary degenerations of the retina. Arch. Ophthalmol. 68:369, 1962.

16. Cunningham, C. A., Friedberg, D. N., and Carr, R. E.: Clofazamine-induced generalized retinal degeneration. Retina 10:131, 1990.

17. Henkind, P., Carr, R. E., and Siegel, I. M.: Early chloroquine retinopathy, clinical and functional findings. Arch. Ophthalmol. 71:157, 1964.

18. Ogden, T. E.: Clinical electrophysiology. In Ryan, S. J., and Ogden, T. E. (eds.): Retina. Basic Science and Inherited Retinal Disease, vol. 1. St. Louis, C. V. Mosby, 1989, pp. 293–294.

19. Gouras, P., and Gunkel, R. D.: EOG in chloroquine and other retinopathies. Arch. Ophthalmol. 70:629, 1963.

20. de Smet, M. D., Rubin, B. I., Belfort, R., Jr., Pizzo, P. A., Mellow, S., and Nussenblatt, R. B.: Retinal manifestations of AIDS in pediatric patients. Ophthalmology 97(suppl.):l53, 1990.

Visual Dysfunction Without Retinitis in Patients With Acquired Immunodeficiency Syndrome

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Patients with human immunodeficiency virus infection may have noninfectious and infectious retinopathies, as well as clinical symptoms consistent with optic nerve dysfunction. Noninfectious acquired immunodeficiency syndrome–related retinopathy is seen in most patients with AIDS. Morphologic studies have shown that the number of retrobulbar optic nerve fibers in patients with AIDS is decreased compared to the number of optic nerve fibers in normal control eyes. To determine whether these patients had a visual dysfunction consistent with damage to the macula and optic nerve, 78 subjects (156 eyes) were studied using color-vision and contrast-sensitivity testing. The Farnsworth-Munsell 100-Hue color-vision test was performed on all subjects and age-corrected color-vision scores for all groups were compared. A significant decrease in color discrimination was found in the patients with AIDS ($P < .001$). Contrast-sensitivity testing disclosed a deficit of contrast threshold in patients with AIDS at four of five spatial frequencies and in patients with AIDS-related complex at three of the five spatial frequencies examined. This study demonstrated a functional visual deficit in eyes without retinitis consistent with dysfunction of the macula or optic nerve in patients with AIDS.

PATIENTS WITH the acquired immunodeficiency syndrome may have ill-defined visual symptoms consistent with dysfunction of the retina or optic nerve, or both, despite having normal visual acuity. To assess this, we performed Farnsworth-Munsell 100-Hue color-vision and contrast-sensitivity tests in human immunodeficiency virus–positive patients with normal Snellen distance and near visual acuity, at various stages of their disease. Cotton-wool spots, the most common manifestation of noninfectious AIDS retinopathy, may be a cause of visual dysfunction; infarctions may permanently damage the regions of nerve fiber layer, retinal ganglion cells, and the inner nuclear layer (Figs. 1 and 2).[1,2] Cotton-wool spots are more common in patients with AIDS than in patients with AIDS-related complex and are uncommon in HIV-positive control subjects. Cotton-wool spots correlate with immune dysfunction, as patients with cotton-wool spots have lower T-helper/suppressor cell ratios and are in more advanced clinical stages of HIV infection.[3,4] We examined optic nerves of patients with AIDS in the laboratory and found preliminary evidence of a loss of axons even in eyes without infectious retinitis.[5,6] We wished to determine whether psychophysical tests would support our hypothesis that HIV-infected patients do develop measurable loss of visual function as their disease progresses.

Subjects and Methods

We selected 78 men between 25 and 49 years of age and classified them in one of four groups

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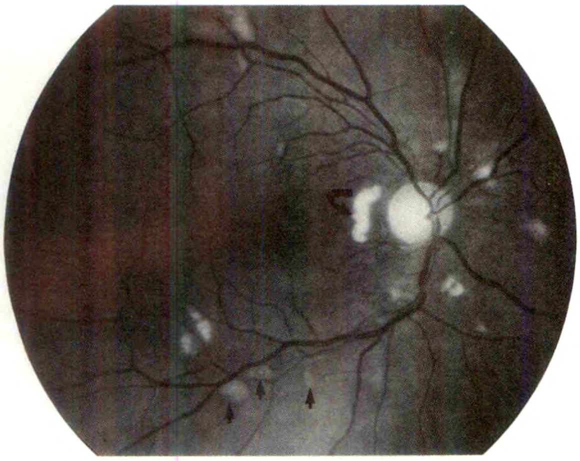

Fig. 1 (Quiceno and associates). Human immunodeficiency virus retinopathy showing cotton-wool spots at different stages of evolution. The large lesion located temporal to the optic disk (curved arrow) is a newly formed cotton-wool spot. The white areas just below the inferotemporal vein (small arrows) are older cotton-wool spots that have begun to fade, and which will eventually be undetectable by ophthalmoscopy.

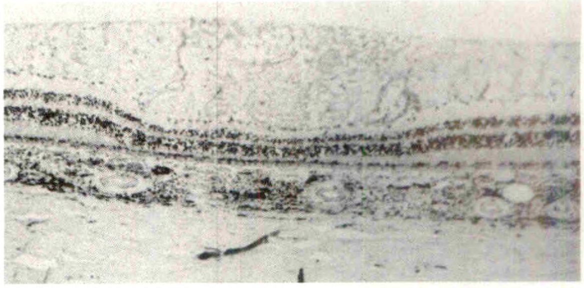

Fig. 2 (Quiceno and associates). Light-microscopic appearance of cotton-wool spots, corresponding to infarction of the inner retina. The axoplasm has become swollen and the ganglion cells and inner nuclear layer are permanently damaged.

according to the Centers for Disease Control.[7] Eighteen of the 78 subjects (23.1%) were healthy (HIV-negative); 19 (24.4%) were HIV-positive but asymptomatic (Centers for Disease Control group II); 20 (25.6%) were patients with AIDS-related complex who had persistent generalized lymphadenopathy (Centers for Disease Control group III) or oral hairy leukoplakia, herpes zoster, or oral candidiasis (Centers for Disease Control group IVc-2); and 21 (26.9%) had AIDS with defining opportunistic infections (Centers for Disease Control group IVc-1) or with Kaposi's sarcoma or non-Hodgkin's lymphoma (Centers for Disease Control group IVd). All subjects were selected from our medical center population and were screened to ensure that only patients without a history of organic eye disease or ocular complaints would be studied. Both eyes of each patient (156 total eyes) were evaluated. After testing visual acuity, only subjects with a best-corrected Snellen visual acuity of 20/20 or better were included. All subjects underwent an initial ocular slit-lamp examination and indirect ophthalmoscopy after full dilation of the pupils, to rule out any clinically apparent ocular disease. All patients in the HIV-negative control group had a history of normal results of eye examinations, and screening penlight examinations of the anterior segment. Of the study patients, those with cytomegalovirus retinitis, *Pneumocystis carinii* choroiditis, toxic maculopathy, diabetic retinopathy, and other organic disease were excluded from our trial. However, patients with HIV-related retinopathy (cotton-wool spots and hemorrhage) were included. Fundus photography was performed and diagrams were made of all lesions.

See also p. 14

Before considering patients for our study, we screened them for ingestion of drugs that could have caused retinal toxicity[8,9] and eliminated other systemic causes of acquired color-vision changes.[9] Patients were carefully questioned and medical histories were taken to ensure that patients with clinically apparent AIDS-related dementia, patients who were uncooperative, or patients who were too ill to perform the psychophysical tests were excluded from the study. All visual function tests were performed using the patient's best ophthalmic near refraction. All the subjects viewed the Ishihara pseudoisochromatic plates (1985, 24 plates edition) under 1,200-lux standardized light conditions. Subjects who had evidence of congenital color-vision abnormalities were not considered for further testing. We administered the Farnsworth-Munsell 100-Hue test to all subjects using the Macbeth easel lamp with an illumination of 300 lux, under conditions similar to those used by Verriest, Van Laethem, and Uvijls[10] in their study of 232 normal individuals. In our study, every eye was tested individually, and the right eye was tested first. No time limit was prescribed for the duration of the Farnsworth-Munsell test, and subjects were allowed to arrange the chips until complete satisfaction. After completion of the test, we calculated the total error score, the square root of the error score,[10] and the axis.[11] The square root of the color-vision score was age-corrected by normalizing it to the age-corrected normal scores as determined by Verriest, Van Laethem, and Uvijls.[10] The mean of the difference in error score for each eye from the normal subjects was calculated and the square-root error score was analyzed. These data were identical to those of our own controls.

A contrast-sensitivity test was performed on all subjects under standard conditions (30 to 70 foot-lamberts). Each eye was tested separately, with the right eye being tested first. We asked the subjects to read the contrast sensitivity (VCTS 6000, Vistech Consultants, Inc., Dayton, Ohio) chart system at a distance of 16 inches. Each chart was composed of five rows representing low to high spatial frequencies (from 1.5 cycles per degree to 18 cycles per degree). Across the chart from left to right were patches containing sinusoidal gratings of progressively less contrast in various orientations. The patient viewed the chart and identified the orientation of each grating. The information was used to generate a two-dimensional graph that described the contrast sensitivity with each spatial frequency. The assessment took two to three minutes.

Statistical analysis included multivariate analysis of variance to make intergroup and age comparisons. When an overall difference was detected, Duncan's multiple range test was applied to delineate specific group differences. A P value less than or equal to .05 was considered significant. All data analysis was performed using the Statistical Analysis Software general linear models procedure (SAS Institute, Cary, North Carolina) and all data were determined as the mean ± the standard deviation.

The contrast-sensitivity value at each spatial frequency was analyzed in each of the four patient groups (including the control group). A nonparametric test, the Kruskal-Wallis test, was used to compare the study groups at each spatial frequency to evaluate the homogeneity of the groups and the Duncan's multiple-range test was applied to evaluate for group differences.[12,13]

Results

All patients completed the psychophysical testing satisfactorily. The mean age of the healthy control subjects was 33.1 ± 8.5 years; the mean age for HIV-positive patients was 37.6 ± 8.3 years; the mean age for patients with AIDS-related complex was 38 ± 6.8 years; and the mean age for the patients with AIDS was 37 ± 7.1 years. Age was not statistically significant between the study groups. The average time of performance for the Farnsworth-Munsell 100-Hue test for both eyes was 30 minutes. The times of performance of this test were not significantly different among the four study groups. The square-root error scores of the Farnsworth-Munsell 100-Hue test in patients with AIDS were significantly higher than those of patients with AIDS-related complex, or HIV-positive or HIV-negative patients ($P < .001$; Table 1). This difference remained highly significant, whether the right eye, the left eye, or the mean of scores of both eyes was analyzed. Similarly, the method of age correction using our control subjects or the control subjects of Verriest, Van Laethem, and Uvijls[10] did not change the outcome. Color-vision scores were not significantly different between any of the other groups studied. No particular axis of error was identified in the patients with AIDS.

Contrast-sensitivity studies were analyzed by comparing the numerical contrast-sensitivity values at each of five spatial frequencies (1.5, 3, 6, 12, and 18 cycles per degree). There was a statistically significant deficit in contrast-sensitivity values at 3, 6, 12, and 18 cycles per degree for patients with AIDS compared to those of the healthy control group ($P < .01$). Patients with AIDS-related complex also had

TABLE 1

RESULTS OF AGE-CORRECTED COLOR-VISION TEST OF STUDY PATIENTS (SQUARE ROOT OF TOTAL ERROR SCORE OF FARNSWORTH-MUNSELL 100-HUE COLOR TEST)

PATIENT GROUP	R.E., MEAN ± STANDARD DEVIATION	L.E., MEAN ± STANDARD DEVIATION
Normal control patients	5.16 ± 2.37	5.35 ± 2.18
HIV-positive patients	5.73 ± 2.25	6.06 ± 2.39
Patients with AIDS-related complex	5.70 ± 2.67	5.78 ± 2.68
Patients with AIDS	9.79 ± 2.65*	9.74 ± 2.82*

*The patients with AIDS had a higher error score in both eyes than any of the other groups ($P < .001$).

TABLE 2

MEANS OF CONTRAST SENSITIVITY VALUES (OF BOTH EYES) AT FIVE SPATIAL FREQUENCIES FOR THE FOUR STUDY GROUPS*

	1.5 CYCLES PER DEGREE	3 CYCLES PER DEGREE	6 CYCLES PER DEGREE	12 CYCLES PER DEGREE	18 CYCLES PER DEGREE
Normal control patients	45.97	109.92	120.28	91.61	29.00
HIV-positive patients	47.60	86.47	90.97	72.25	24.44
Patients with AIDS-related complex	39.86	81.67	82.78[†]	62.86[‡]	21.06[†]
Patients with AIDS	40.83	77.19[‡]	75.40[‡]	55.10[‡]	17.36[‡]

*Comparisons were significant at the .01 and .05 levels as determined by the Kruskal-Wallis nonparametric test of homogeneity and Duncan's multiple range test. These differences remained significant whether the right eye, the left eye, or the mean score of both eyes was analyzed.

[†] $P < .05$.

[‡] $P < .01$.

significantly lower contrast-sensitivity values compared with those of the normal control group at 6 and 18 cycles per degree ($P < .05$) and 12 cycles per degree ($P < .01$). The difference remained highly significant whether the score of the right eye, the left eye, or the average score of both eyes was analyzed (Table 2).

Discussion

In this study, patients with AIDS had significant visual impairments in color vision and contrast sensitivity. Previous studies have shown that axonal degeneration and an associated decrease in the number of optic nerve axons can be found in patients with AIDS.[5,6] Previous cross-sectional observational studies have shown that infarctions of the nerve fiber layer develop in most patients with AIDS and that the total number of such infarctions increases over time.[3,14-16] These nerve fiber layer lesions may result in accumulation of nerve fiber layer infarctions and may be the basis of our histologic findings of loss of optic nerve axons. Alternatively, our psychophysical findings may have been the result of a primary optic neuropathy.

We have observed that some HIV-infected patients, despite having normal visual acuity, describe visual symptoms suggestive of disruption of the optic nerve or other visual pathways. We hypothesized that these complaints may have been related to the microvascular retinopathy (cotton-wool patches) seen in patients with AIDS and to a lesser degree, in patients with AIDS-related complex. This retinopathy has been well described by our group and by others[4] and is known to become more prevalent in the later stages of HIV infection. We studied functional visual deficits related to AIDS retinopathy or optic neuropathy. If retinopathy is the cause of the functional visual loss in this study, it would have profound implications because the prevalence of this retinopathy approaches 100% in patients with AIDS. As patients with AIDS survive longer, the visual loss from retina–optic nerve pathway dysfunction may become clinically more significant.

We documented visual impairment in color vision and contrast sensitivity. The group with AIDS had a marked deficit of contrast sensitivity at all but the lowest spatial frequency tested. No difference was found at 1.5 cycles per degree; this spatial frequency may be less sensitive for optic nerve dysfunction. The patients with AIDS-related complex had a significant deficit of contrast sensitivity at the three highest of the five spatial frequencies tested. Color vision and contrast sensitivity were affected in these patients, which was consistent with inner nuclear retinal damage. Both of these tests measure primarily P-cell function; thus, we have documented damage to the P-cell system. Sparing of the lowest spatial frequency contrast sensitivities may reflect the insensitivity of the test. This does not rule out damage to the subpopulation of ganglion cells that project to magnocellular layers of the lateral geniculate body (M cells). Sensitive tests that specifically challenge M-cell function should be performed to clarify the degree of M-cell damage in this disease.[17-20]

Patients who did not have confounding diseases or treatments that might have resulted in reduced visual function were carefully selected. Organic causes of retinal disease and inherited color-vision loss were eliminated and undemented patients who had intact cerebral function were carefully selected. Screening was first performed with the Ishihara color-vision test to eliminate congenitally color-deficient patients; it is possible that this screening also eliminated patients with more severe acquired color-vision dysfunction from our study population, leading to an underestimate of the losses in color vision in AIDS. The lack of a specific axis is common in patients with acquired color-vision deficiencies.[21] The time required to complete the Farnsworth 100-Hue test was not different in any of our study groups. This made it unlikely that other diseases of the central nervous system might have accounted for the higher error score.

The changes observed here in psychophysical test results and the decrease in optic nerve axon counts that we have documented in a related study[5,6] may have been caused by the cumulative effect of nerve fiber layer infarcts in the retina and resultant degeneration and loss of optic nerve axons or as a result of a primary optic neuropathy. It is uncertain whether the process causing retinal nerve fiber layer infarctions or primary optic neuropathy is directly caused by HIV infection, or is a consequence of other AIDS-related processes. Therapeutic interventions may become available to prevent this form of visual loss in patients with more advanced stages of HIV infection. It is also intriguing that some psychophysical testing (contrast sensitivity at 6, 12, and 18 cycles per degree) indicates damage to the visual system in patients with AIDS-related complex before the onset of AIDS; such tests may have important diagnostic and prognostic implications. As patients with AIDS continue to survive longer, the visual loss that we documented may become more clinically significant and may require therapeutic intervention. Further study of these psychophysical phenomena and correlation with neurologic testing, magnetic resonance imaging, and immunologic and virologic studies of these patients[22] will help delineate the pathophysiologic and therapeutic modalities involved in visual dysfunction without retinitis in patients with AIDS.

References

1. Murataand, M., and Yoshimoto, H.: Morphological study of the pathogenesis of retinal cotton wool spots. Jpn. J. Ophthalmol. 27:362, 1983.
2. Chihara, E.: Pathogenesis of cotton wool patches. A clinical study. Jpn. J. Ophthalmol. 27:397, 1983.
3. Freeman, W. R., Chen, A., Henderly, D. E., Levine, A. M., Luttrull, J. K., Urrea, P. T., Arthur, J., Rasheed, S., Cohen, J. L., Neuberg, D., and Leung, R. J.: Prevalence and significance of acquired immunodeficiency syndrome related retinal microvasculopathy. A cross sectional observational study. Am. J. Ophthalmol. 107:229, 1989.
4. Jabs, D. A., Green, W. R., Fox, R., Polk, F., and Barlett, J. G.: Ocular manifestations of acquired immune deficiency syndrome. Ophthalmology 96:1092, 1989.
5. Sadun, A. A., Tenhula, W. N., and Heller, K. B.: Optic nerve pathology associated with AIDS. Ultrastructural changes. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 1792.
6. Tenhula, W. N., Sadun, A. A., Heller, K. B., and Xu, S. Z.: Optic nerve axon losses in AIDS. Morphometric comparisons. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 1793.
7. Centers for Disease Control: Classification system for human lymphotropic virus type III-lymphadenopathy associated virus infections. M.M.W.R. 35:334, 1986.
8. Swartz, M.: Other disease. Drug toxicity and metabolic and nutritional conditions. In Ryan, S. (ed.): Retina, vol. 2. St. Louis, C. V. Mosby, 1989, pp. 737–743.
9. Birch, J., Chrisholm, C. A., Kinnear, P., Marre, M., Pinckers, A. J. L. G., Pokorny, J., Smith, V. C., and Verriest, G.: Acquired color vision defects. In Pokorny, J., Smith, V. C., Verriest, G., and Pinckers, A. J. L. G. (eds.): Congenital Acquired Color Vision Deficits. Current Ophthalmology Monographs. New York, Grune and Stratton, 1979, pp. 243–348.
10. Verriest, G., Van Laethem, J., and Uvijls, A.: A new assessment of the normal ranges of the Farnsworth-Munsell 100-Hue test scores. Am. J. Ophthalmol. 93:635, 1982.
11. Smith, V. C., Pokorny, J., and Pass, A. S.: Color-axis determination on the Farnsworth-Munsell 100-Hue test. Am. J. Ophthalmol. 100:176, 1985.
12. Gibbons, J. D.: Non-parametric Statistical Inference. New York, McGraw-Hill Book Company, 1971, pp. 98–201.

13. Siegel, S.: Nonparametric Statistics. New York, McGraw-Hill Book Company, 1956, pp. 184–194.

14. Freeman, W. R., Lerner, C. W., Mines, J. A., Lash, R. S., Nadel, A. J., Starr, M. B., and Tapper, M. L.: A prospective study of the ophthalmologic findings in the acquired immune deficiency syndrome. Am. J. Ophthalmol. 97:133, 1984.

15. Freeman, W. R., and O'Connor, G. R.: Acquired immune deficiency syndrome retinopathy, pneumocystis, and cotton wool spots. Am. J. Ophthalmol. 98:235, 1984.

16. Freeman, W. R., and Helm, M.: Retinal and ophthalmologic manifestations of AIDS. In Ryan, S. J. (ed.): Retina, vol. 2. St. Louis, C. V. Mosby, 1989, pp. 597–613.

17. Livingstone, M. S., and Hubel, D. H.: Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. J. Neurosci. 7:3416, 1987.

18. Kupersmith, M. J., Holopigian, K., and Seiple, W. H.: Contrast sensitivity testing. In Wall, M., and Sadun, A. A. (eds.): New Methods of Sensory Visual Testing. New York, Springer-Verlag, 1989, pp. 53–63.

19. Owsley, C., Sekuler, R., and Siemsen, D.: Contrast sensitivity throughout adulthood. Vision Res. 23:689, 1983.

20. Schiller, P. H., Logothetis, N. K., and Charles, E. R.: Functions of the colour-opponent and broadband channels of the visual system. Nature 343.68, 1990.

21. Pokorny, J., Smith, V. C., Verriest, G., and Pinckers, A. J. L. G. (eds.): Congenital Acquired Color Vision Deficits. Current Ophthalmology Monographs. New York, Grune and Stratton, 1979.

22. Koralink, I. J., Beaumanoir, A., Hausler, R., Kohler, A., Safran, A. B., Delacous, R., Vibert, D., Mayer, E., Burkhard, P., Nahory, A., Magistris, M. R., Sanches, J., Meyers, P., Paccolat, F., Quolex, F., Gabriel, V., Perrin, L., Mermillod, B., Gauther, G., Waldvogel, F. A., and Hirschel, B.: A controlled study of early neurologic abnormalities in men with asymptomatic human immunodeficiency virus infection. N. Engl. J. Med. 323:864, 1990.

OPHTHALMIC MINIATURE

His most striking feature was his eyes. They were not unattractive; he suffered from exophthalmos, and his protruding eyeballs seem to have surveyed the world with a supercilious, offensive stare. His walrus mustache draws attention to a large head set on a short, frail body. He looks pompous, curt, and rude. And so he was, to those who bored him.

William R. Manchester, *The Last Lion, Winston Spencer Churchill*
Boston, Little, Brown & Company, 1983, p. 95

Morphometric Comparisons of Optic Nerve Axon Loss in Acquired Immunodeficiency Syndrome

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Axonal degeneration and diminution of the axonal population in the optic nerve have been documented in aging and in various neuro-ophthalmic conditions. We applied morphometric techniques to the postmortem examination of optic nerves obtained from patients with acquired immunodeficiency syndrome. Twelve optic nerves (eight from patients with AIDS and four from age-matched control eyes) were stained with paraphenylenediamine and morphometrically analyzed with a computer-assisted image and measurement system. Degeneration was often severe and was scattered throughout all of the AIDS-affected optic nerves. In the AIDS-affected optic nerves, the mean axonal population was markedly lower than the mean obtained from normal optic nerves (880,000 vs 1,507,000). Despite the approximate 40% loss of axons, mean axonal diameters were not markedly different, suggesting that no particular class of axon was especially susceptible to AIDS-associated degeneration. The extent and pattern of axonal loss in optic nerves of patients with AIDS suggest that the changes may not only be secondary to damage at the retina, but may reflect an AIDS-associated primary optic neuropathy.

CHANGES IN the morphometry of the human optic nerve have been described in the normal optic nerve as a function of age[1-4] and in diseases such as Alzheimer's disease[5-9] and chronic glaucoma.[10-13] Many studies have been performed on the clinical ophthalmic findings in AIDS,[14-22] including optic neuritis[22]; however, quantitative histopathologic analysis has been lacking.

See also p. 8

The acquired immunodeficiency syndrome can affect all organs of the body, including the eyes and the central nervous system. An investigation of the effect of AIDS on the optic nerve may further the understanding of both ophthalmic and neurologic issues. Ninety percent of patients with AIDS are estimated to have neurologic findings at autopsy, although only about one half of the findings are detected clinically.[23] Although neurologic lesions in patients with AIDS may be the result of lymphomas or opportunistic infections, evidence of direct damage by the virus to the central nervous system is scarce. Up to 75% of patients with AIDS seen at autopsy[17] have ocular findings attributable to AIDS, whereas clinical reports of ocular signs of AIDS at initial examinations range from 50% to 73%.[14,15,17] The four most common ocular findings are cotton-wool spots (nerve fiber layer infarcts), cytomegalovirus retinitis, conjunctival Kaposi's sarcoma, and neuro-ophthalmic motility abnormalities.[17] Isolated retinal hemorrhages, acute retinal necrosis, and cranial nerve palsies have also been reported.[14]

Previous studies suggested that cotton-wool spots and isolated retinal hemorrhages do not seem to be the result of an infectious agent, but rather are direct manifestations of AIDS itself.[14 17,24-26] To rule out the possibility of secondary damage caused by infection, specimens from patients whose history included oppor-

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tunistic infections related to the eye, such as cytomegalovirus retinitis, were excluded from our study. The purpose of our study was to establish the extent of optic nerve axonal damage in patients with AIDS.

Patients and Methods

Cross sections of eight optic nerves from eight patients with AIDS and four optic nerves from four normal age-matched control eyes were morphometrically analyzed. The optic nerves to be used for our study were selected randomly from each patient. Patients whose history included opportunistic infections related to the eye, such as cytomegalovirus retinitis, were excluded from our study. All eyes were examined grossly after removing the superior colotte. Examination of retinal tissue was performed with a dissecting microscope, and any lesions seen were examined further with special stains. The average age of the patients with AIDS was 39.4 ± 5.9 years (range, 31 to 51 years). The average age of the control patients was 46.5 ± 14.7 years (range, 32 to 64 years). The ages of the patients with AIDS and control patients were not significantly different ($P = .247$, unpaired t-test). Each optic nerve was sectioned, fixed in mixed aldehydes, osmicated, dehydrated, and embedded in plastic. Sections 1 μm thick were cut on an ultramicrotome and stained with 1% paraphenylenediamine in methanol solution.[27,28]

Images of each optic nerve cross section were divided into 16 sectors of approximately equal area with the aid of a camera lucida. Nerve

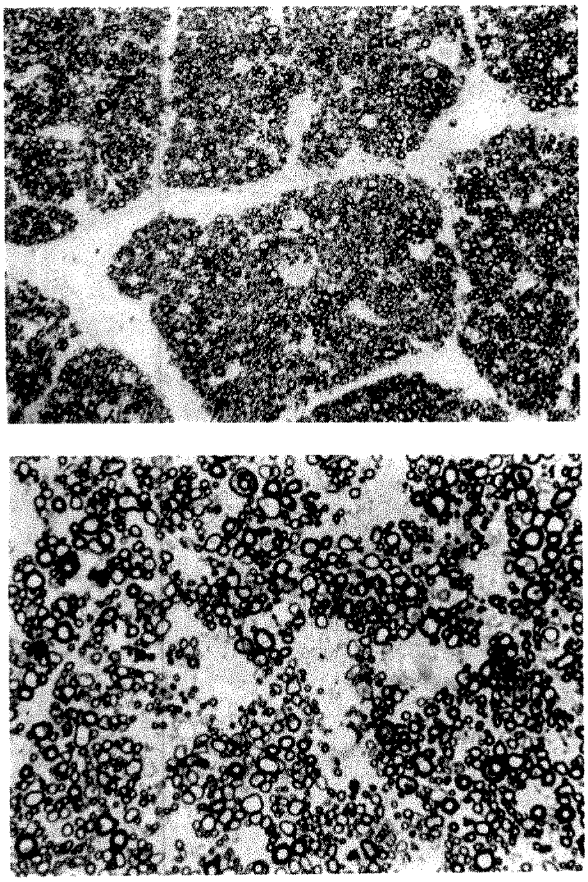

Fig. 1 (Tenhula and associates). Top, Cross section of normal optic nerve (paraphenylenediamine, × 170). Bottom, Higher magnification of cross section of normal optic nerve (paraphenylenediamine, × 425). Normal axons appear as annuli, as the paraphenylenediamine stains only the myelin rings.

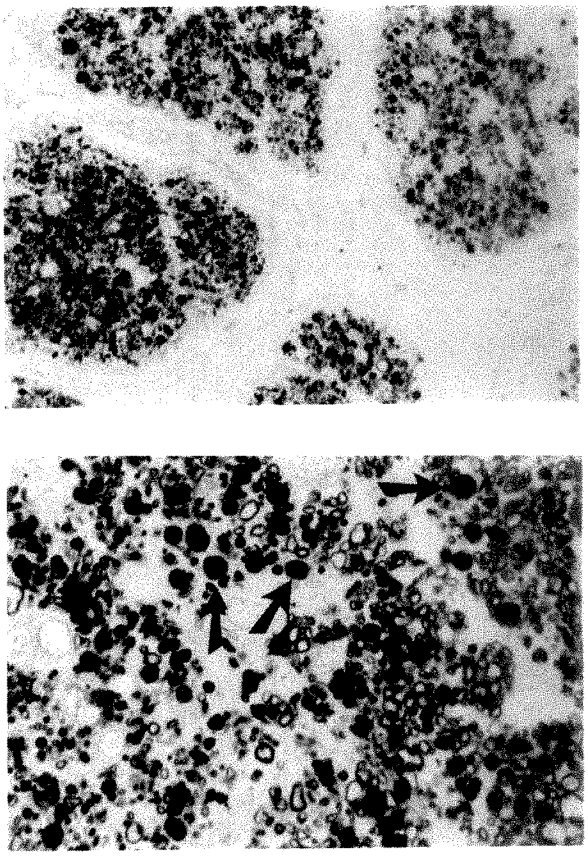

Fig. 2 (Tenhula and associates). Top, Cross section of optic nerve from a patient with AIDS (paraphenylenediamine, × 170). Bottom, Higher magnification of cross section of optic nerve from a patient with AIDS (paraphenylenediamine, × 425). Axonal degeneration is seen as dark profiles (arrows) interspersed between normal axons.

fibers were randomly counted in each of the 16 sectors. In each sector area, axon diameter was measured and a histogram of these measurements was obtained. Optic nerve density was calculated from the number of axons per sector area and total axon population was estimated by using the total nerve area and the average fiber densities. The profiles of degenerated axons were also counted and measured in both AIDS and normal optic nerve specimens.

We performed our analyses on a semiautomated image analysis system, which used a microscope with an attached high-resolution video camera and was interfaced with an enhanced Apple Macintosh IIcx computer. The computer digitized and processed the image. This image enhancement and analysis software allowed us to count and measure both intact and degenerated axon profiles in a reliable manner. The user interacted with the computerized system to ensure that fibers that may have been overlooked by the computer were accurately counted and measured. To test the reliability of our method, three of the 12 nerves were quantitatively studied and were counted on two separate occasions, by two different technicians. The results obtained by each technician consistently varied by less than 5%. The axon populations were plotted and had a gaussian distribution. Therefore, we applied the unpaired *t*-test to test for differences between control and experimental nerves.

Results

Gross and light-microscopic examination of the retinas from the eight patients with AIDS demonstrated retinal nerve fiber layer infarcts in six patients. Cytomegalovirus or other infectious retinitis was not evident.

In the normal optic nerves, few or no degenerated profiles were observed (Fig. 1). All eight optic nerves from patients with AIDS had axonal degeneration. The degeneration in the optic nerves of patients with AIDS varied from moderate to severe (Fig. 2). Large aggregates of diffuse degeneration were scattered throughout the optic nerve. No particular sector of the nerve appeared to be consistently more affected in patients with AIDS. To quantitate the presence of degeneration, we calculated the mean number of degenerated profiles per 100 intact axons. In control specimens, the percentage ranged from 0.5 to 1.8 degenerated profiles per 100 normal profiles; in AIDS specimens, the percentage ranged from 4.3 to 11.1 degenerated profiles per 100 normal profiles (Tables 1 and 2). The mean was 6.6% ± 2.3%, which was significantly higher than the 1.0% ± 0.6% calculated for the control optic nerves ($P = .001$, unpaired *t*-test; Table 3).

In AIDS-affected optic nerves, the mean axon population and the mean axon density values were significantly less than in the normal optic nerves that were analyzed ($P = .006$ and $P = .003$, respectively, unpaired *t*-test; Table 3). The mean axon population in the AIDS-affected optic nerves was 880,073 ± 199,616, compared to 1,507,117 ± 443,123 for the normal control optic nerves (Tables 1 and 2), suggesting a loss of approximately 42% of optic nerve fibers in the patients with AIDS. In the most severe case of optic nerve degeneration in AIDS, the axon population was depleted by 56% of the normal mean value. In the specimens obtained from patients with AIDS, the mean axon density value was 179.3 ± 30.4 axons per 1,000 μm^2, whereas in controls, the mean axon density value was 252.0 ± 27.8 (Table 3).

The mean diameters of axons in AIDS-affected optic nerves were not significantly different from mean diameters of axons in normal optic nerves ($P = .269$, unpaired *t*-test; Table 3). The mean axon diameter in patients with AIDS was 0.92 ± 0.10 μm; in the control optic nerves the mean axon diameter was 0.86 ± 0.10 μm (Tables 1 and 2). Just as in histograms of axon diameters in normal optic nerves, the histogram of axon diameters in AIDS-affected optic nerves had a peak around 0.7 μm and a smaller peak of larger caliber axons at around 1.5 μm.

Discussion

The 1% paraphenylenediamine staining technique and computer-assisted image analysis techniques allowed us to quantitate the presence of degeneration, the reflected loss of axonal population, and the consequent decrease in mean axon density in optic nerves obtained from patients with AIDS. Compared to normal age-matched control optic nerve fibers, the average loss was approximately 40% of AIDS optic nerve fibers. The profiles of degenerated axons were scattered throughout the optic nerve and represented all stages of the degenerative process. It is important to distinguish damage caused by local effects from damage secondary to injury at another level such as the

TABLE 1
AXON POPULATION AND DEGENERATION RATIOS OF NORMAL CONTROL OPTIC NERVES

PATIENT NO.	AGE (YRS)	TOTAL AXON POPULATION	MEAN DEGENERATION RATIO*
1	53	1,018,762	1.8 ± 0.5
2	64	1,253,377	1.0 ± 0.4
3	32	1,951,813	0.7 ± 0.6
4	37	1,804,515	0.5 ± 0.5
Mean	46.5	1,507,117	1.0
S.D.	14.7	443,123	0.6

*Mean degeneration ratio equals the number of degenerated profiles per 100 intact axons.

nerve fiber layer of the retina in the optic nerves of patients with AIDS. Our gross and histologic examination of the retinas of these patients disclosed no evidence of cytomegalovirus or other infectious retinitis. Nerve fiber layer infarcts resolve with time; it is likely that all of our patients had nerve fiber layer infarcts before death.[14,15,17]

Normal aging and diseases such as glaucoma and Alzheimer's disease may cause certain sizes of axons or specific areas of the optic nerve to have reduced nerve fiber populations and densities. Johnson, Miao, and Sadun[4] and Sadun, Johnson, and Miao[5] suggested a general loss of axons across all sizes with age. The optic nerves obtained from older subjects had markedly fewer axons than did those of young subjects, but no particular-size subpopulation was affected by changes caused by age.[4,5] After correcting for differences caused by time to fixation, Balazsi and associates[2] estimated a loss of over 5,000 axons per year over the age span of their sample. Regression analysis by Repka and Quigley[1] estimated a loss of fibers of only 6% over 75 years, whereas data from Balazsi and associates[2] suggested a loss of 33% of fibers in a lifetime of 75 years.

To control for this possible variation, we matched the ages of normal control subjects as closely as possible to the ages of the patients with AIDS used in our study. The mean age of our control subjects was higher than that of the patients with AIDS. Therefore, if the effect of age on nerve fiber count in the normal population was significant, our results may mask even more severe damage caused by AIDS than we were able to illustrate.

In addition to possible general effects of aging on the optic nerve, chronic glaucoma has also been demonstrated to damage particular

TABLE 2
AXON POPULATION AND DEGENERATION RATIOS OF OPTIC NERVES FROM PATIENTS WITH AIDS

PATIENT NO.	AGE (YRS)	TOTAL AXON POPULATION	MEAN DEGENERATION RATIO*
1	38	1,226,692	4.3 ± 1.1
2	38	1,089,995	6.0 ± 1.6
3	38	982,199	5.6 ± 1.4
4	31	827,074	5.1 ± 1.7
5	43	656,741	11.1 ± 5.8
6	35	777,286	8.6 ± 2.1
7	41	771,606	4.7 ± 1.2
8	51	708,991	7.1 ± 3.9
Mean	39.4	880,073	6.6
S.D.	5.9	199,616	2.3

*Mean degeneration ratio equals the number of degenerated profiles per 100 intact axons.

TABLE 3
MORPHOMETRIC DATA FROM OPTIC NERVES OF NORMAL CONTROL EYES AND PATIENTS WITH AIDS

	CONTROL EYES (N = 4)	PATIENTS WITH AIDS (N = 8)	UNPAIRED *T*-TEST	P VALUE
Total axon population (axons)	1,507,117 ± 443,123	880,073 ± 199,616	−3.48	.006
Axon density (axons/1000 μm^2)	252.0 ± 27.8	179.3 ± 30.4	−4.00	.003
Degeneration (profiles/100 intact axons)	1.0 ± 0.6	6.6 ± 2.3	4.67	.001
Axonal diameter (μm)	0.86 ± 0.1	0.92 ± 0.1	1.17	.269

selective regions of the optic nerve[12,13] and induce a selective loss of fibers greater than the mean.[12] This suggests there is a subtype of retinal ganglion cells that is more susceptible to damage caused by intraocular pressure.[12,13] Sadun and Bassi[6] and Hinton and associates[7] have described optic nerve degeneration in patients with Alzheimer's disease. In addition to finding an overall decrease in axon density and population, Sadun and Bassi[6] found evidence of a predominant dropout of the largest class of retinal ganglion cell (M cell) fibers in patients with Alzheimer's disease compared to the cell fibers of age-matched controls. Our findings indicated no predilection for a particular-size subpopulation of axon or a specific region of the optic nerve directly damaged in patients with AIDS, as opposed to patients with glaucoma[12] or Alzheimer's disease.[6] The histograms of the nerve fiber spectra illustrated that all sizes of axons were involved in the degenerative processes in patients with AIDS.

Studies of normal optic nerves show a large variation between individuals and even between eyes of the same individual, regardless of age.[12] Absolute fiber counts and diameter measurements also vary from laboratory to laboratory, which is caused by differences in equipment and operators. For example, Repka and Quigley[1] reported a mean fiber count of 693,316 and a mean axon diameter of 0.96 μm, whereas previous studies from our laboratory demonstrated considerably higher total fiber counts of 1,685,000 and mean axon diameters of about 0.81 μm.[6] Repka and Quigley[1] conceded that their automated counting and measuring method missed the smallest axons and probably caused their absolute numbers to be relative underestimates of actual nerve fiber populations. The semiautomated computer-assisted technique used in our laboratory allowed the operator to interact with the computer and count and measure by hand small or irregular axons that would have been missed by a totally automated system.

Several infectious agents cause ocular lesions in patients with AIDS. These include, most commonly, cytomegalovirus retinitis, pneumocystosis, cryptococcal meningitis, and toxoplasmosis.[14,16,17] The most common ocular manifestations of AIDS, however, are nerve fiber layer infarcts (cotton-wool spots), which do not appear to be caused by an infectious agent.[14,17,24-26] Because visual loss is not usually attributed to these transient ischemic infarcts, it is difficult to estimate how many patients with AIDS have unreported and undetected nerve fiber layer infarcts, especially if a patient is only examined once.[14-26] Up to 50% of the population with AIDS demonstrates cotton-wool spots on one fundus examination and over the course of the disease, it is likely that all patients with AIDS will have developed multiple cotton-wool spots.[20]

Our study showed that even without opportunistic infections, damage to the optic nerve of patients with AIDS still occurs. In the anterior (or retrobulbar) portion of the optic nerve, the discrete bundles of axons correspond to the segregation of axons in the nerve fiber layer of the retina. Therefore, if degeneration in the optic nerve is attributable to a few focal nerve fiber layer infarcts, we would expect to see small isolated clusters of degenerated axons in the retrobulbar optic nerve. Conversely, our study showed larger diffuse clusters of degeneration, which suggested either that the damage was primary to the optic nerve, or secondary to multifocal damage at many different locations in the retina.

Our study introduced evidence for direct degeneration of retinal ganglion cell axons in the optic nerve without opportunistic infection. Our results could not distinguish between the possibilities that the changes were either secondary to multiple cotton-wool spots or other damage at the retinal level, or were an uncharacterized effect of the human immunodeficiency virus on the central nervous system. The mechanism of the degenerative process in the optic nerve of patients with AIDS has yet to be determined. Axons in the optic nerve might be injured as a consequence of specific or nonspecific alterations in the immune system.

Clinically, our study reminded us that even with marked axonal loss, visual acuity may remain normal. Thus, visual acuity remains good in the face of advanced visual loss from glaucoma or Alzheimer's disease.[8,10,12] Acquired immunodeficiency syndrome–associated optic neuropathy may not be detected in patients with a standard ophthalmic examination. However, as patients with AIDS live longer, it is likely that the process of axonal loss, whether the cumulative effect of multiple nerve fiber layer infarcts, or a primary axonal degeneration within the optic nerve, will progress. We may anticipate, therefore, that the clinical effects of such degeneration will become more pronounced in the future. Such patients should be assessed using the complete armamentarium of psychophysical tests recently made available.

References

1. Repka, M. X., and Quigley, H. A.: The effect of age on normal human optic nerve fiber number and diameter. Ophthalmology 96:26, 1989.

2. Balazsi, A. G., Rootman, J., Drance, S. M., Schulzer, M., and Douglas, G. R.: The effect of age on the nerve fiber population of the human optic nerve. Am. J. Ophthalmol. 97:760, 1984.

3. Giarelli, L., Grandi, G., Delendi, M., and Falconieri, G.: The pathology of optic nerve aging. Metab. Pediatr. Systemic Ophthalmol. 12:61, 1989.

4. Johnson, B. M., Miao, M., and Sadun, A. A.: Age-related decline of human optic nerve axon populations. Age 10:5, 1987.

5. Sadun, A. A., Johnson, B. M., and Miao, M.: Axon caliber populations in the human optic nerve. Changes with age and disease. Highlights in Neuro-ophthalmology. In Proceedings of the Sixth Meeting of the International Neuro-Ophthalmology Society, Hakone, Japan, 1986, p. 15.

6. Sadun, A. A., and Bassi, C. J.: Optic nerve damage in Alzheimer's disease. Ophthalmology 97:9, 1990.

7. Hinton, D. R., Sadun, A. A., Blanks, J. C., and Miller, C. A.: Optic-nerve degeneration in Alzheimer's disease. N. Engl. J. Med. 315:485, 1986.

8. Sadun, A. A., Borchert, M., DeVita, E., Hinton, D. R., and Bassi, C. J.: Assessment of visual impairment in patients with Alzheimer's disease. Am. J. Ophthalmol. 104:113, 1987.

9. Sadun, A. A.: Assessing vision in patients with Alzheimer's disease. West. J. Med. 148:693, 1988.

10. ———: The optic neuropathy of Alzheimer's disease. Metabol. Pediatr. Systemic Ophthalmol. 12:64, 1989.

11. Quigley, H. A., Addicks, E. M., and Green, W. R.: Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch. Ophthalmol. 100:135, 1982.

12. Quigley, H. A., Dunkelberger, G. R., and Green, W. R.: Chronic human glaucoma causing selectively greater loss of large optic nerve fibers. Ophthalmology 95:357, 1988.

13. Quigley, H. A., Sanchez, R. M., Dunkelberger, G. R., L'Hernault, N. L., and Baginski, T. A.: Chronic glaucoma selectively damages large optic nerve fibers. Invest. Ophthalmol. Vis. Sci. 28:913, 1987.

14. Freeman, W. R., Lerner, C. W., Mines, J. A., Lash, R. S., Nadel, A. J., Starr, M. B., and Tapper, M. L.: A prospective study of the ophthalmologic findings in the acquired immunodeficiency syndrome. Am. J. Ophthalmol. 97:133, 1984.

15. Holland, G. N., Pepose, J. S., Petit, T. H., Gottlieb, M. S., Yee, R. D., and Foos, R. Y.: Acquired immune deficiency syndrome. Ocular manifestations. Ophthalmology 90:859, 1983.

16. Lipson, B. K., Freeman, W. R., Beniz, J., Goldbaum, M. H., Hesselink, J. R., Weinreb, R. N., and Sadun, A. A.: Optic neuropathy associated with cryptococcal arachnoiditis in AIDS patients. Am. J. Ophthalmol. 107:523, 1989.

17. Palestine, A. G., Rodrigues, M. M., Macher, A. M., Chan, C. C., Longo, D., Reichert, C. M., Steis, R., Rook, A. H., and Nussenblatt, R. B.: Ophthalmic involvement in acquired immunodeficiency syndrome. Ophthalmology 91:1092, 1984.

18. Newsome, D. A., Green, W. R., Miller, E. D., Kiessling, L. A., Morgan, B., Jabs, D. A., and Polk, B. F.: Microvascular aspects of acquired immune deficiency syndrome retinopathy. Am. J. Ophthalmol. 98:590, 1984.

19. Pepose, J. S., Hilborne, L. H., Cancilla, P. A., and Foos, R. Y.: Concurrent herpes simplex and cytomegalovirus retinitis and encephalitis in the acquired immune deficiency syndrome (AIDS). Ophthalmology 91:1669, 1984.

20. Rosenberg, P. R., Uliss, A. E., Friedland, G. H., Harris, C. A., Small, C. B., and Klein, R. S.: Acquired immunodeficiency syndrome. Ophthalmic manifestations in ambulatory patients. Ophthalmology 90:874, 1983.

21. Grossniklaus, H. E., Frank, K. E., and Tomsak, R. L.: Cytomegalovirus retinitis and optic neuritis in acquired immune deficiency syndrome. Report of a case. Ophthalmology 94:1601, 1987.

22. Gross, J. G., Sadun, A. A., Wiley, C. A., and Freeman, W. R.: Severe visual loss related to isolated peripapillary retinal and optic nerve head cytomegalovirus infection. Am. J. Ophthalmol. 108:691, 1989.

23. Petito, C. K., Cho, E. S., Lemann, W., Navia, B. A., and Price, R. W.: Neuropathology of acquired

immunodeficiency syndrome (AIDS). An autopsy review. J. Neuropathol. Exp. Neurol. 45:635, 1986.

24. Holland, G. N., Gottlieb, M. S., and Foos, R. Y.: Retinal cotton-wool patches in acquired immunodeficiency syndrome. N. Engl. J. Med. 307:1704, 1982.

25. Pepose, J. S., Nestor, M. S., Holland, G. N., Cochran, A. J., and Foos, R. Y.: An analysis of retinal cotton-wool spots and cytomegalovirus retinitis in the acquired immunodeficiency syndrome, correspondence. Am. J. Ophthalmol. 95:118, 1983.

26. Freeman, W. R., Chen, A., Henderly, D. E., Levine, A. M., Luttrul, J. K., Urrea, P. T., Arthur, J., Rasheed, S., Cohen, J. L., Neuberg, D., and Leung, R. J.: Prevalence and significance of acquired immunodeficiency syndrome-related retinal microvasculopathy. Am. J. Ophthalmol. 107:229, 1989.

27. Sadun, A. A., and Schaechter, J. D.: Tracing axons in the human brain. A method utilizing light and TEM techniques. J. Electron Microsc. Tech. 2:175, 1985.

28. Sadun, A. A., Smith, L. E., and Kenyon, K. R.: Paraphenylenediamine. A new method for tracing human visual pathways. J. Neuropathol. Exp. Neurol. 42:200, 1983.

Repair of Retinitis-related Retinal Detachments With Silicone Oil in Patients With Acquired Immunodeficiency Syndrome

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To provide prompt visual rehabilitation and to reduce the need for repeated operations, we performed vitrectomy with silicone oil tamponade in 16 consecutive eyes with retinal detachments related to cytomegalovirus retinitis and acute retinal necrosis in 13 patients with acquired immunodeficiency syndrome. In all 16 eyes (100%), retinas were reattached with one operation. Preservation of ambulatory vision was achieved in six of eight eyes (75%; mean follow-up, 14.6 weeks). No patient with hand motion visual acuity or worse preoperatively recovered ambulatory vision. Visual acuity recovery was limited by optic nerve disease in five eyes (31%). Silicone oil-related side effects did not adversely affect visual outcome in any eye. Six patients (46%) have since died (mean, 4.4 months postoperatively). These data indicated that successful surgical repair of these detachments can be consistently achieved with this approach. The prognosis for ambulatory vision is strongly related to preoperative visual acuity.

CYTOMEGALOVIRUS RETINITIS is the most commonly recognized opportunistic infection of the posterior segment in patients with acquired immunodeficiency syndrome. It develops in approximately 25% of patients at some time during the course of their disease.[1-4] Despite the availability of effective medical treatment with the antiviral drug, ganciclovir, an incidence of subsequent rhegmatogenous retinal detachment is reported in 15% to 29% of treated eyes.[3,5-8] The cumulative probability of retinal detachment one year after the diagnosis of cytomegalovirus retinitis is 50%.[8] The detachments typically involve large areas of thinned necrotic retina and feature multiple posterior holes that make reattachment difficult.

Recently, the acute retinal necrosis syndrome has been described in patients with AIDS.[5,9-12] As with the classic form that was originally described in healthy patients, herpes simplex virus and varicella-zoster virus have been implicated as etiologic agents.[12,13] Rhegmatogenous retinal detachments occur in 50% to 84% of immunocompetent patients with acute retinal necrosis.[14-16] Although no data are available on acute retinal necrosis in immunodeficient patients, a rapidly progressive course and a high rate of detachments are suggested.[5,9,11,12] Similar to the detachments associated with cytomegalovirus retinitis, multiple holes in conjunction with large areas of retinal necrosis are usually encountered.

Our initial experience with these types of complex retinal detachments showed a high rate of persistent or recurrent detachments when repaired by scleral buckling, vitrectomy with gas injection, or both. Methods using some form of internal retinal tamponade yield higher primary reattachment rates and lower reoperation rates.[17,18] The use of silicone oil in this setting has been particularly encouraging. Several reports on cytomegalovirus-related rhegmatogenous retinal detachments described successful reattachment of the retina in most if not all patients.[5-8,19] Visual acuity was often stabilized or improved, and anterior segment complications were surprisingly uncommon. A similar surgical approach with acute retinal necrosis–related retinal detachments in immu-

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nocompromised patients has had comparable anatomic success.[5,9] Because of the high potential for success with one operation, many surgeons now use silicone oil with the primary procedure to repair these complex detachments.

To provide prompt visual rehabilitation and to reduce the need for repeated operations in this group of patients, we repaired rhegmatogenous retinal detachments secondary to the two types of necrotizing retinitis described previously with vitrectomy and silicone oil in 16 consecutive cases at our institution. Our study emphasized surgical technique, visual acuity outcome, and postoperative course of disease with this approach.

Patients and Methods

Pars plana vitrectomy and silicone oil infusion were used to repair 16 consecutive rhegmatogenous retinal detachments caused by necrotizing retinitis associated with AIDS at our institution between October 1988 and October 1990. The 16 eyes were in 13 men, all of whom were seropositive for the human immunodeficiency virus. The average age was 36 years (range, 19 to 54 years). The postoperative follow-up period ranged from five to 32 weeks, with a mean of 14.6 weeks.

Included in the study were patients in whom AIDS was diagnosed and who subsequently developed cytomegalovirus retinitis or the acute retinal necrosis syndrome. (No other causes of opportunistic infection and rhegmatogenous retinal detachment were encountered.) The ocular diagnosis was based on clinical criteria in all cases. The fundus appearance of cytomegalovirus retinitis comprised multiple distinct areas of white, granular retinal opacification with irregular feathered borders often mixed with retinal hemorrhages. The necrotic areas typically initiated along the major vascular arcades in the posterior pole and enlarged and coalesced with time. The characteristic findings of the acute retinal necrosis syndrome were multiple white opaque patches of thickened retina in the periphery, which rapidly coalesced and extended posteriorly. Retinal arteriolar sheathing and retinal hemorrhages were often seen later in the course of disease.

Detailed fundus drawings were used to document the changes and to monitor the pre- and postoperative course of disease. Proliferative vitreoretinopathy was noted and graded preoperatively using the classification system of the Retina Society Terminology Committee.[20]

Induction medical treatment with intravenous administration of ganciclovir (6 to 10 mg/kg of body weight/day) was begun preoperatively for active cytomegalovirus retinitis if not already initiated and continued postoperatively for a minimum of two weeks until the retinitis stabilized. Outpatient maintenance with intravenous administration of ganciclovir, coordinated by the patient's primary-care provider, was used in most cases. Ganciclovir was not administered intravitreously in any of the cases. No patient in this study was treated with foscarnet.

High-dose acyclovir (1,500 mg/m^2/day) was administered intravenously to patients with the acute retinal necrosis syndrome to treat the presumed herpes simplex or varicella-zoster infection. Intravenous administration of acyclovir was continued postoperatively in patients with active retinitis or optic nerve disease. Corticosteroids and anticoagulants were not administered systemically. Barrier photocoagulation was used in the two eyes that initially had active retinitis before the development of the retinal detachment.

Optic nerve disease is a potential complicating factor in cytomegalovirus retinitis and acute retinal necrosis. Absolute and relative criteria for retinitis-associated optic neuropathy established by Sergott and associates[21] were used in this study. The absolute criteria included any of the following findings that were not consistent with the retinal changes: afferent pupillary defect, visual acuity or visual field changes, and sudden deterioration in visual acuity over a 24- to 36-hour period. The relative criteria included optic disk edema and enlarged optic nerves disclosed by computed tomography or B-scan ultrasonography. All patients were carefully monitored to detect pre- and postoperative optic nerve disease.

The criteria for retinal detachment repair using vitrectomy and silicone oil were as follows: (1) rhegmatogenous retinal detachments involving or threatening the macula, (2) peripheral rhegmatogenous retinal detachments with profound loss of visual acuity in the fellow eye, and (3) health status commensurate with reasonable longevity. Excluded were detachments considered to be amenable to simple scleral-buckling procedures and eyes that had no preoperative light perception. Five of the 13 patients had bilateral retinal detachments, giving a total of 18 detachments. Two eyes were excluded and not repaired because they had no light perception, leaving a total of 16 study eyes. Informed consent for vitrectomy with silicone oil was obtained from all patients.

Vitrectomy was performed with local anesthesia attained in seven eyes and general anesthesia attained in nine eyes using a standard bimanual, three-port technique and 20-gauge vitrectomy surgical instruments. Removal of all vitreous cortex was attempted. Membrane peeling was used when necessary (Cases 5 and 10). An air-fluid exchange with internal drainage of subretinal fluid was performed to flatten the retina initially in nine eyes, succeeded by air–silicone oil (1,000 or 5,000 centistokes) exchange with drainage of any small amount of remaining subretinal fluid. In seven eyes, a direct fluid-oil exchange was performed. With either approach, drainage of subretinal fluid was performed through preexisting retinal breaks when possible. Argon laser endophotocoagulation was used in all cases, and was applied in a triple-row fashion along all breaks and zones of retinitis or necrosis. Lensectomy was needed in Cases 5 and 10 because preexisting cataracts precluded adequate visualization. Scleral buckling was not used in any eye. Undiluted vitreous and retinal biopsy specimens were obtained intraoperatively in four cases (Cases 1, 3, 8, and 9) and sent for viral culturing (cytomegalovirus, herpes simplex virus, and varicella-zoster virus). No medications were administered intravitreously during or after the operation.

Results

Cytomegalovirus retinitis was diagnosed in 11 of the 16 eyes (69%). Acute retinal necrosis from presumed herpes simplex or zoster viruses was diagnosed in five eyes (31%; Table). The diagnosis was based on the previously described clinical criteria. In one patient (Case 3), the culture was cytomegalovirus positive. The other three retinal cultures were negative. All four vitreous cultures were negative.

Active retinitis was seen to some degree at the time of diagnosis of the retinal detachment in all but two patients (Cases 5 and 11). The retinitis stabilized postoperatively in all eyes except one (Case 6). In this eye, recurrent cytomegalovirus retinitis developed approximately three months postoperatively and was considered to have affected the visual result adversely because of macular involvement.

Preoperative visual acuity ranged from 20/20 to light perception with ambulatory vision (5/200 or better) in eight of the 16 eyes (50%). Three of the five eyes (60%) with the acute retinal necrosis syndrome and five of the 11 eyes (45%) with cytomegalovirus retinopathy had ambulatory vision preoperatively. One patient had clinically evident optic nerve disease with light perception visual acuity preoperatively (Case 3) and underwent investigational intraoperative optic nerve sheath decompression. (Although some data suggest a beneficial effect of this procedure on visual outcome in optic neuritis related to acute retinal necrosis,[21] no such data are currently available with cytomegalovirus-related optic neuropathy.)

Fourteen of the 16 operated-on eyes were repaired using this technique as the initial procedure. Two eyes (Cases 5 and 6) were operated on eight and two weeks, respectively, after failed vitrectomy with perfluorocarbon gas infusion. Mild proliferative vitreoretinopathy (Retina Society Classification Grade C1) was noted in two eyes (Cases 5 and 10). No marked proliferative vitreoretinopathy was encountered in any other eye.

Complete retinal reattachment was achieved in all eyes (100%) with the initial vitrectomy and silicone oil procedure. No recurrent retinal detachments were experienced and no additional operations or procedures were performed during the follow-up period. Silicone oil was left in place in all patients. Postoperative ambulatory vision was preserved in six of eight eyes (75%) at the end of follow-up (two cases of acute retinal necrosis and four cases of cytomegalovirus retinitis). No patient with visual acuity of hand motion or worse recovered ambulatory vision.

Marked optic nerve disease was encountered in five of the 16 (31%) eyes (two with acute retinal necrosis and three with cytomegalovirus retinitis). Poor visual acuity resulted in all eyes (four with no light perception and one with hand motion). As noted earlier, optic nerve sheath decompression was performed on one eye (Case 3) in conjunction with the vitreous operation in an attempt to improve or preserve visual acuity. Despite the operation and continued medical treatment with parenterally administered ganciclovir for documented cytomegalovirus infection, visual acuity declined to no light perception by three months postoperatively.

TABLE
SUMMARY OF ALL CASES OF RETINAL DETACHMENT ASSOCIATED WITH AIDS

CASE NO., AGE (YRS), GENDER	DIAGNOSIS*	MEDICAL TREATMENT	EYE	VISUAL ACUITY†		POSTOPERATIVE COMPLICATIONS	FOLLOW-UP (WKS)
				PREOPERATIVE	POSTOPERATIVE		
1, 49, M	Acute retinal necrosis	Acyclovir	R.E.	H.M.	N.L.P.	Optic nerve disease and cataract	24
2, 33, M	Acute retinal necrosis	Acyclovir	R.E.	20/40	20/100	—	12
3, 33, M	Cytomegalovirus	Ganciclovir	L.E.	L.P.	N.L.P.	Optic nerve disease	12
4, 54, M	Cytomegalovirus	Ganciclovir	L.E.	H.M.	L.P.	Cataract	10
5, 36, M	Cytomegalovirus	Ganciclovir	R.E.	H.M.	H.M.	—	24
6, 19, M	Cytomegalovirus	Ganciclovir	R.E.	H.M.	H.M.	Recurrent retinitis	8
7, 34, M	Acute retinal necrosis	Acyclovir	L.E.	5/200	5/200	—	14
8, 20, M	Acute retinal necrosis	Acyclovir	R.E.	20/200	N.L.P.	Optic nerve disease	12
9, 41, M	Acute retinal necrosis	Acyclovir	L.E	L.P.	L.P.	—	8
10, 41, M	Cytomegalovirus	Ganciclovir	R.E.	L.P.	N.L.P.	Optic nerve disease	32
11, 41, M	Cytomegalovirus	Ganciclovir	L.E.	20/50	5/200	—	5
12, 36, M	Cytomegalovirus	Ganciclovir	R.E.	20/30	20/400	—	10
13, 36, M	Cytomegalovirus	Ganciclovir	L.E.	L.P.	L.P.	—	10
14, 30, M	Cytomegalovirus	Ganciclovir	L.E.	5/200	20/200	—	15
15, 48, M	Cytomegalovirus	Ganciclovir	L.E.	20/20	L.P.	Optic nerve disease	10
16, 33, M	Cytomegalovirus	Ganciclovir	R.E.	20/25	20/100	—	28

*Type of retinitis diagnosed preoperatively.

†H.M. indicates hand motion, L.P. indicates light perception, and N.L.P. indicates no light perception.

Minor posterior subcapsular cataracts formed in only two eyes (Cases 1 and 4) and did not appear to have a marked impact on the final visual acuity. All lenses were clear preoperatively except in two eyes, both of which required lensectomy at the time of the initial silicone oil procedure. No keratopathy, glaucoma, or other silicone oil–related complication was seen in any eye.

Six of the 13 patients (46%) died of complications related to AIDS. Death occurred with a mean time of 18 postoperative weeks (range, ten to 28 weeks). Four patients had cytomegalovirus retinitis and two had the acute retinal necrosis syndrome. Three of the six patients (50%) had evidence of optic nerve disease in one or both eyes.

Discussion

Cytomegalovirus retinitis and acute retinal necrosis can lead to rhegmatogenous retinal detachments in patients with AIDS. Of all forms of necrotizing retinopathies seen in our patients, cytomegalovirus retinitis accounted for most of the rhegmatogenous retinal detachments. Cytomegalovirus retinitis was diagnosed in 69% of the eyes in our study. This distribution was comparable to that in a recent report in which 75% of the detachments were related to cytomegalovirus retinopathy.[5] This most likely reflects a greater incidence of cytomegalovirus retinopathy compared to acute retinal necrosis in AIDS. Of the 130 patients with AIDS examined consecutively by Sidikaro and associates,[5] 60 of the 68 patients with necrotizing retinal infections had cytomegalovirus retinopathy and only three had acute retinal necrosis (five had *Toxoplasma*-induced retinochoroiditis).

From a surgical standpoint, we grouped these detachments because they possessed similar characteristics. Typically, both have posterior breaks that are often multiple and large and are located at the border or within areas of thin, necrotic retina. Cytomegalovirus retinitis usually involves minimal vitreous cellular infiltrate and traction. Although acute retinal necrosis typically involves moderate to severe vitreitis and anterior chamber reaction, acute retinal necrosis in immunosuppressed patients generally induces much less intraocular inflammation.[5,9] Rhegmatogenous retinal detachments tend to occur late in the course of both forms of retinitis as zones of markedly thinned, atrophic retina develop.

Vitrectomy with gas tamponade with or without scleral buckling is often performed first to repair such retinal detachments, but problems with redetachment are frequently encountered that necessitate multiple operations to achieve anatomic success.[15,18] The use of silicone oil provided long-term internal tamponade and was particularly useful for repairing the complex rhegmatogenous retinal detachments in our study. Patients with AIDS typically have marked systemic morbidity and limited life expectancy. With a single surgical procedure, the use of silicone oil has the potential to provide immediate visual function and unrestricted postoperative ambulation, in addition to permanent reattachment, and is therefore more advantageous than the use of gas. If scleral buckling is not performed, the procedure is greatly simplified. Overall, total surgical manipulation of the eye can be minimized, benefiting both patient and health care provider.

The long-term anatomic success rate was 100% in our study and no repeated detachment operations or other intraocular procedures were needed. Similar anatomic results were encountered in several other reports.[5-9,19] Freeman and associates[6] used pars plana vitrectomy and silicone oil injection to repair rhegmatogenous retinal detachments associated with cytomegalovirus retinitis in 1987. Their data suggested a promising outcome with visual acuity improving in five of seven cases but data on the postoperative course were limited. A larger, more recent study on retinal detachments from cytomegalovirus retinitis by Jabs and associates[8] demonstrated a 70% reattachment rate with silicone oil compared to 0% with the nonsilicone oil surgical procedures. Visual results were not as encouraging, with only 20% of the patients with retinal detachments repaired with silicone oil developing ambulatory vision. Forster and associates[9] reported two cases of acute retinal necrosis with secondary rhegmatogenous retinal detachments in patients with AIDS. Both detachments were successfully repaired in a similar fashion with the visual acuity improving from hand motion to counting fingers at two months postoperatively in the first patient and declining from 20/30 to 20/60 (by potential acuity meter) at six weeks postoperatively in the second patient. Sidikaro and associates[5] successfully repaired three rhegmatogenous retinal detachments from acute retinal necrosis in patients with AIDS using silicone oil, but postoperative visual acuity was no light perception in all three patients.

In our study, ambulatory vision was preserved in 12 of the 16 eyes (75%). The deterioration in visual acuity to worse than 5/200 in two eyes was considered to be caused by optic nerve disease and not surgical or silicone oil complications. In both eyes, visual acuity initially stabilized in the ambulatory range, then subsequently deteriorated about two months postoperatively. Theoretically, this deterioration may represent a toxic effect of silicone oil, but such an abrupt, profound reduction in visual acuity has not been evident in other extensive studies of patients treated with silicone oil.[22-24] Additionally, optic nerve dysfunction was clinically evident.

The visual acuity of patients with preoperative visual acuities of hand motion or worse did not improve. These patients typically had more extensive necrosis and larger detachments (with the macula detached in all cases). Some degree of preexisting macular retinitis or subclinical optic nerve disease may explain, at least in part, the poor outcome in this subgroup. Similar results were found in the study by Jabs and associates,[8] in which only four of 14 eyes with retinal detachments involving the macula were successfully repaired by silicone oil and achieved ambulatory vision. Our data suggest that preoperative visual acuity is a prognostic indicator of ultimate visual outcome. This is further supported by the study of Sidikaro and associates,[5] in which the visual acuity of only two of six eyes with nonambulatory vision improved to 5/200 or better.

The potential postoperative complications of silicone oil include glaucoma, cataracts, and keratopathy.[22-27] The only adverse effect we encountered was mild posterior subcapsular cataract in two cases. Although both eyes had poor postoperative visual acuity, the visual acuity had stabilized at that level before the lens changes developed. Furthermore, the degree of cataract formation was mild and probably would not have affected the final visual outcome of any case in this report. The incidence of cataracts with silicone oil is usually high, with changes developing in up to 80% of patients by two years.[23-25] These figures, however, include all degrees of lens changes, even those of minimal visual importance. Although it is certainly possible that more cataractous changes would have been encountered with a longer follow-up period, our data are consistent with the study of Freeman and associates,[6] in which all seven eyes undergoing vitrectomy retained clear lenses with silicone oil, and with the study of Jabs and associates,[8] in which only one cataract was observed in 20 eyes treated with silicone oil. It has been suggested that these lenses may remain clearer than other phakic eyes treated with silicone oil because of the lack of intraocular trauma from multiple surgical procedures.[6] Generally, it is most desirable to leave an eye phakic when lenses remain clear, as it probably reduces the risk of other silicone-oil side effects by preventing oil from entering the anterior chamber.

Optic nerve disease may complicate the course of both acute retinal necrosis and cytomegalovirus retinitis.[6,12,14,16,21,28-32] This was clinically evident in five of the 16 eyes (31%) in this study. It was the greatest single identifiable factor limiting postoperative visual outcome. At the time of the operation, three of the five eyes had advanced retinitis and poor visual acuity despite preoperative treatment with systemic antiviral medication. As noted earlier, two eyes with active retinitis and retinal detachments were not repaired because of preexisting nerve disease and no light perception.

The survival rate after the diagnosis of cytomegalovirus retinitis in ganciclovir-treated patients, although variable, averages seven to eight months.[33,34] Similar survival data on the acute retinal necrosis syndrome associated with AIDS are not available. In our study, six of the 13 patients (46%) died at an average of 18 weeks postoperatively. All deaths were the result of immunodeficiency-related medical problems. These results are comparable to data including both forms of retinitis reported elsewhere in which the median interval from detachment to death was 17 weeks.[5] The severity of retinitis, pre- or postoperative visual acuity, and the presence of optic nerve disease with death could not be correlated in this study.

Although both groups appeared similar in terms of outcome, the small numbers precluded statistical comparison. The disease course of retinal necrosis in the immunosuppressed population is less well known than that of cytomegalovirus retinitis. Forster and associates[9] suggested that the course may be more rapidly progressive than is typically believed, even with early initiation of treatment, and attributed this logically to the altered immune status. The three eyes with acute retinal necrosis noted by Sidikaro and associates[5] had no light perception after retinal detachment operations. Overall, our study suggested comparable long-term visual acuity results and complication rates between the two groups.

We used silicone oil to repair complex rhegmatogenous retinal detachments associated with two similar forms of necrotizing retinitis in AIDS. These detachments can be readily repaired with vitrectomy and primary use of silicone oil in one operation. Scleral buckling and lensectomy are not necessary in most cases. Although visual acuity recovery is unlikely in patients who have poor initial visual acuity, immediate preservation of ambulatory vision can be achieved in most patients who have preoperative ambulatory vision. The optic neuropathy that appears to be related to these forms of retinitis is the major complicating factor affecting visual acuity results. Patient health remains an extremely important consideration in determining whether to proceed with an operation. Medical treatment for retinitis and optic neuritis along with other problems related to the immunodeficiency may improve in the future, allowing such an operation to make an even greater impact on visual acuity rehabilitation.

References

1. Holland, G. N., Pepose, J. S., Pettit, T. H., Gottlieb, M. S., Yee, R. D., and Foos, R. Y.: Acquired immune deficiency syndrome. Ocular manifestations. Ophthalmology 90:859, 1983.
2. Palestine, A. G., Rodrigues, M. M., Macher, A. M., Chan, C., Lane, C., Fauci, A. S., Masur, H., Longo, D., Reichert, C. M., Steis, R., Rook, A. H., and Nussenblatt, R. B.: Ophthalmic involvement in acquired immunodeficiency syndrome. Ophthalmology 91:1092, 1984.
3. Jabs, D. A., Enger, C., and Bartlett, J. G.: Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch. Ophthalmol. 107:75, 1989.
4. Jabs, D. A., Green, W. R., Fox, R., Polk, B. F., and Bartlett, J. G.: Ocular manifestations of acquired immune deficiency syndrome. Ophthalmology 96:1092, 1989.
5. Sidikaro, Y., Silver, L., Holland, G. N., and Kreiger, A. E.: Rhegmatogenous retinal detachments in patients with AIDS and necrotizing retinal infections. Ophthalmology 98:129, 1991.
6. Freeman, W. R., Henderly, D. E., Wan, W. L., Causey, D., Trousdale, M., Green, R. L., and Rao, N. A.: Prevalence, pathophysiology, and treatment of rhegmatogenous retinal detachment in treated cytomegalovirus retinitis. Am. J. Ophthalmol. 103:527, 1987.
7. Orellana, J., Teich, S. A., Lieberman, R. M., Restrepo, S., and Peairs, R.: Treatment of retinal detachments in patients with the acquired immune deficiency syndrome. Ophthalmology 98:939, 1991.

8. Jabs, D. A., Enger, C., Haller, J., and De Bustros, S.: Retinal detachments in patients with cytomegalovirus retinitis. Arch. Ophthalmol. 109:794, 1991.

9. Forster, D. J., Dugel, P. U., Frangieh, G. T., Liggett, P. E., and Rao, N. A.: Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome. Am. J. Ophthalmol. 110:341, 1990.

10. Chess, J., and Marcus, D. M.: Zoster-related bilateral acute retinal necrosis syndrome as presenting sign in AIDS. Ann. Ophthalmol. 20:431, 1988.

11. Jabs, D. A., Schachat, A. P., Liss, R., Knox, D. L., and Michels, R. G.: Presumed varicella zoster retinitis in immunocompromised patients. Retina 7:9, 1987.

12. Freeman, W. R., Thomas, E. L., Rao, N. A., Pepose, J. S., Trousdale, M. D., Howes, E. L., Nadel, A. J., Mines, J. A., and Bowe, B.: Demonstration of herpes group virus in acute retinal necrosis syndrome. Am. J. Ophthalmol. 102:701, 1986.

13. Chambers, R. B., Derick, R. J., Davidorf, F. H., Koletar, S. L., and Dangel, M. E.: Varicella-zoster retinitis in human immunodeficiency virus infection. Arch. Ophthalmol. 107:960, 1989.

14. Fisher, J. P., Lewis, M. L., Blumenkranz, M. S., Culbertson, W. W., Flynn, H. W., Clarkson, J. G., Gass, J. D., and Norton, E. W. D.: The acute retinal necrosis syndrome. Part 1. Clinical manifestations. Ophthalmology 89:1309, 1982.

15. Blumenkranz, M., Culbertson, W. W., Clarkson, J. G., and Dix, R.: Treatment of the acute retinal necrosis syndrome with intravenous acyclovir. Ophthalmology 93:296, 1986.

16. Clarkson, J. G., Blumenkranz, M. S., Culbertson, W. W., Flynn, H. W., and Lewis, M. L.: Retinal detachment following the acute retinal necrosis syndrome. Ophthalmology 91:1665, 1984.

17. Blumenkranz, M., Clarkson, J., Culbertson, W. W., Flynn, H. W., Lewis, M. L., and Moo Young, G. A.: Vitrectomy for retinal detachment associated with acute retinal necrosis. Am. J. Ophthalmol. 106:426, 1988.

18. ———: Visual results and complications after retinal reattachment in the acute retinal necrosis syndrome. Retina 9:170, 1989.

19. Nagelberg, H. P., Fischer, D. H., and Belmont, J.: Intraocular surgery and the repair of retinal detachments from AIDS-related diseases. Trans. Pa. Acad. Ophthalmol. Otolaryngol. 40:809, 1989.

20. The Retina Society Terminology Committee: The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 90:121, 1983.

21. Sergott, R. C., Anand, R., Belmont, J. B., Fischer, D. H., Bosley, T. M., and Savino, P. J.: Acute retinal necrosis neuropathy. Arch. Ophthalmol. 107:692, 1989.

22. Chan, C., and Okun, E.: The question of ocular tolerance to intravitreal liquid silicone. A long-term analysis. Ophthalmology 93:651, 1986.

23. Haut, J., Ullern, M., Chermet, M., and Van Effenterre, G.: Complications of intraocular injections of silicone combined with vitrectomy. Ophthalmologica 180:29, 1980.

24. Federman, J. L., and Schubert, H. D.: Complications associated with the use of silicone oil in 150 eyes after retina-vitreous surgery. Ophthalmology 95:870, 1988.

25. McCuen, B. W., DeJuan, E., Landers, M. B., and Machemer, R.: Silicone oil in vitreoretinal surgery. Part 2. Results and complications. Retina 5:198, 1985.

26. Gonvers, M.: Temporary silicone oil tamponade in the management of retinal detachment with proliferative vitreoretinopathy. Am. J. Ophthalmol. 100:239, 1985.

27. Haut, J., Larricart, J. P., Van Effenterre, G., and Pinon-Pignero, F.: Some of the most important properties of silicone oil to explain its action. Ophthalmologica 191:150, 1985.

28. Sergott, R. C., Belmont, J. B., Savino, P. J., Fischer, D. H., Bosley, T. M., and Schatz, N. J.: Optic nerve involvement in the acute retinal necrosis syndrome. Arch. Ophthalmol. 103:1160, 1985.

29. Winwood, K. E., Hamed, L. M., and Glaser, J. S.: The spectrum of optic nerve disease in human immunodeficiency virus infection. Am. J. Ophthalmol. 107:373, 1989.

30. Friedman, A. H.: The retinal lesions of the acquired immunodeficiency syndrome. Trans. Am. Ophthalmol. Soc. 82:447, 1984.

31. Marmor, M. F., Egbert, P. R., Egbert, B. M., and Marmor, J. B.: Optic nerve head involvement with cytomegalovirus in an adult with lymphoma. Arch. Ophthalmol. 96:1252, 1978.

32. Litoff, D., and Catalano, R. A.: Herpes zoster optic neuritis in human immunodeficiency virus infection. Arch. Ophthalmol. 108:782, 1990.

33. Gross, J. G., Bozzette, S. A., Mathews, W. C., Spector, S. A., Abramson, I. S., McCutchan, J. A., Mendez, T., Munguia, D., and Freeman, W. R.: Longitudinal study of cytomegalovirus retinitis in acquired immune deficiency syndrome. Ophthalmology 97:681, 1990.

34. Holland, G. N., Sison, R. F., Jatulis, D. E., Haslop, M. G., Sakamoto, M. J., and Wheeler, N. C.: Survival of patients with the acquired immune deficiency syndrome after development of cytomegalovirus retinopathy. Ophthalmology 97:204, 1990.

Severe Periphlebitis, Peripheral Retinal Ischemia, and Preretinal Neovascularization in Patients With Multiple Sclerosis

Andrew K. Vine, M.D.

Two patients with definite multiple sclerosis and marked retinal periphlebitis developed occlusive peripheral retinal vasculitis, which resulted in peripheral retinal ischemia and peripheral retinal neovascularization. Results of investigation for other causes of peripheral proliferative retinopathies were negative in both patients although one patient had a positive anticardiolipin antibody. Both patients have been followed up for over seven years and have maintained good visual acuity with mild regression of the preretinal neovascularization without laser intervention. An analysis of these two cases and six other reported cases indicates that severe periphlebitis can evolve into occlusive peripheral vasculitis, which results in peripheral retinal neovascularization in patients with multiple sclerosis.

VARIOUS OCULAR inflammatory[1-3] changes have been described in patients with multiple sclerosis including optic neuritis, periphlebitis, peripheral uveitis, nongranulomatous and granulomatous iridocyclitis, and posterior uveitis. The reported frequency[4] of these inflammatory conditions has varied markedly. In general, a relatively low incidence of these conditions has been found when reviewing cases in patients with definite multiple sclerosis without specific ocular complaints. In the series of 50 consecutive patients with definite multiple sclerosis described by Graham and associates,[5] only nine patients (18%) had evidence of ocular inflammation, primarily venous sheathing or cuffing. Similarly, in a review of 93 autopsy eyes[6] from patients with definite multiple sclerosis, retinal periphlebitis was found in only seven eyes (8.5%). I treated two patients with definite multiple sclerosis who showed severe periphlebitis and developed occlusive peripheral retinal vasculitis, which resulted in peripheral retinal ischemia and preretinal neovascularization.

Case Reports

Case 1

A 30-year-old white woman was initially examined in September 1983 for uveitis involving the left eye. Her medical history disclosed that she had initially developed optic neuritis of the left eye at age 18 years, and multiple sclerosis as defined by established criteria[7] was subsequently diagnosed. A magnetic resonance imaging scan showed increased signal in the periventricular white matter and in the right thalamus, compatible with a demyelinating process. Examination of cerebrospinal fluid showed oligoclonal bands. Initial examination disclosed a visual acuity of R.E.: 20/20 and L.E.: 20/25. The right anterior chamber showed no cell or flare and the left anterior chamber showed mild cell and flare. Ophthalmoscopy of the right eye disclosed marked focal sheathing of the peripheral retinal veins for 360 degrees. The left eye also showed marked venous sheathing with a large area of white, bloodless, retinal blood vessels involving the superotemporal peripheral retina and a single large frond of elevated preretinal neovascularization. There was no inflammatory material over the inferior ora serrata in either eye. A fluorescein angiogram confirmed that the preretinal neovascularization (Fig. 1) was located at the border between vascularized and avascularized

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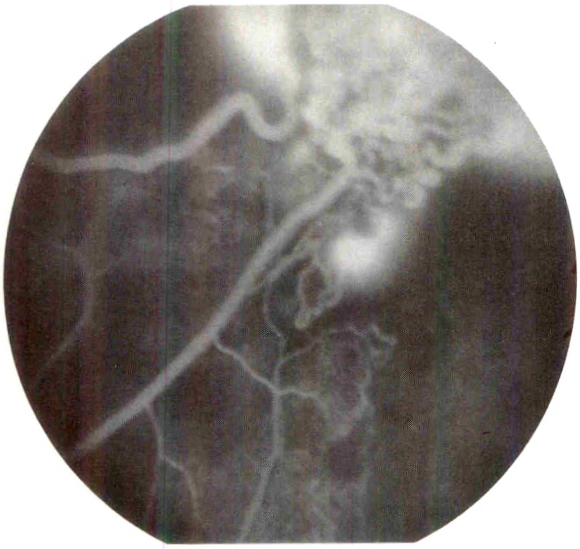

Fig. 1 (Vine). Case 1. Arteriolar venous phase of fluorescein angiogram of superotemporal peripheral retina of left eye shows large frond of elevated preretinal neovascularization at border between vascularized and nonvascularized retina.

retina. Initial laboratory investigation included a nonreactive Venereal Disease Research Laboratory test, a negative antinuclear antibody serum titer, negative cold agglutinins, normal protein electrophoresis, normal results of thoracic radiography, and normal serum glucose. The patient was normotensive.

The left eye was initially treated with topical corticosteroid eyedrops, and the patient was subsequently monitored periodically for evidence of progression of her bilateral vasculitis and uniocular uveitis. Over the succeeding years, the patient has developed increasing vitreitis of the left eye with resulting macular edema, bilateral anterior granulomatous uveitis (Fig. 2), and recurrent optic neuritis involving the left eye. These developments have required intermittent topical, periocular, and oral corticosteroid therapy. During follow-up assessment, the degree of retinal vascular occlusion remained unchanged and there was gradual increasing gliosis of the elevated preretinal neovascularization without laser intervention. In 1990, a positive anticardiolipin antibody of the IgM class was identified, and the patient was started on low-dose aspirin therapy because she had no other evidence of vascular occlusions or a history of spontaneous abortions.

In April 1991, visual acuity was R.E.: 20/20 and L.E.: 20/20. Ophthalmoscopy of the right eye showed only a few vitreous cells and resolution of the previous diffuse venous sheathing. The left eye also showed minimal vitreous cells and a similar degree of ischemic retina in the superotemporal equatorial area. The elevated preretinal neovascularization was markedly gliotic.

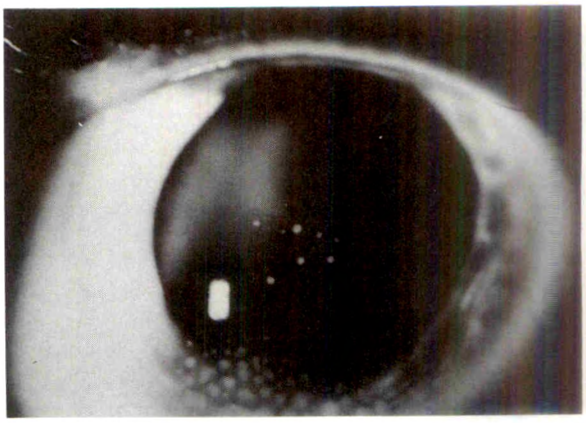

Fig. 2 (Vine). Case 1. Anterior segment of right eye shows numerous mutton-fat keratic precipitates on central and inferior corneal endothelium.

Case 2

A 40-year-old white woman was initially referred in April 1984 because of bilateral uveitis. She had a history of multiple episodes of focal neurologic loss and was presently unable to walk because of severe leg weakness and ataxia. Best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/50. Biomicroscopy showed mild cell in the anterior chamber of each eye. Fundus examination of the right eye disclosed mild vitreous cells, mild macular edema, and marked focal sheathing of the retinal veins. Ophthalmoscopy of the left eye disclosed moderate vitreous cells, moderate macular edema, similar diffuse focal sheathing of the retinal veins, and numerous focal accumulation of inflammatory debris suspended in the vitreous above the superotemporal arcade. The inferior pars plana showed no abnormality bilaterally. Fluorescein angiography showed numerous foci of vascular leakage corresponding to areas of periphlebitis (Fig. 3).

Initial laboratory investigation included a complete blood cell count, sedimentation rate, Venereal Disease Research Laboratory test, antinuclear antibody serum titer, serum protein electrophoresis, and thoracic radiography. Results of all were either normal or nonreactive. The blood pressure was normal. A neurologic assessment confirmed the diagnosis of definite

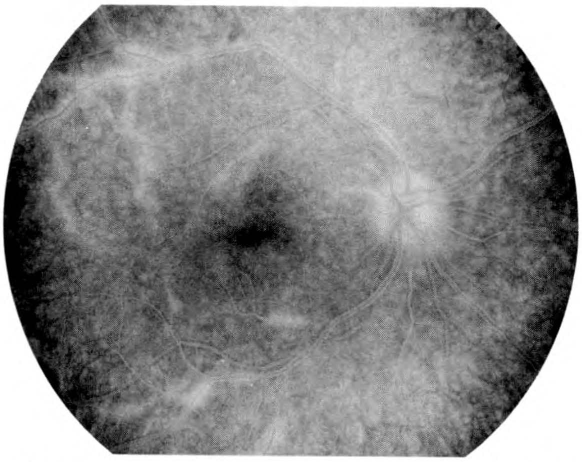

Fig. 3 (Vine). Case 2. Arteriolar venous phase of fluorescein angiogram of right eye shows numerous foci of focal leakage of fluorescein corresponding to areas of periphlebitis.

multiple sclerosis,[7] on the basis of the clinical findings and a magnetic resonance imaging scan, which showed evidence of demyelination in the paraventricular areas.

In January 1986, visual acuity was 20/50 in each eye. Ophthalmoscopy showed bilateral inferior peripheral retinal ischemia with fronds of preretinal neovascularization. A fluorescein angiogram confirmed that the preretinal neovascularization (Fig. 4) was located at the junction between vascularized and avascularized retina. Additional investigation included prothrombin and partial thromboplastin time tests. Results of both were normal. Lupus anticoagulant and anticardiolipin antibody testing was negative.

Over the following years, both eyes were intermittently treated with periocular corticosteroids or prednisone was administered orally to the patient to control fluctuating macular edema. In August 1986, the right eye underwent an extracapsular cataract extraction for an increasing posterior subcapsular opacity.

In June 1991, visual acuity was R.E.: 20/30 and L.E.: 20/40−2. Both eyes continued to show minimal vitreitis. The degree of peripheral inferior retinal ischemia was unchanged but the foci of preretinal neovascularization had somewhat regressed.

Discussion

In 1960, François, Asseman, and Leroyer[8] reported three cases in the French ophthalmic literature of patients who had multiple sclerosis and developed vitreous hemorrhages secondary to peripheral preretinal neovascularization. One of the three patients was described as having severe periphlebitis, but in two of the patients vitreous hemorrhage appeared to prevent detailed examination of the fundus. Other causes of peripheral retinal neovascularization in these patients were not clearly ruled out in this report. Fifteen years later, Morse[9] described a 52-year-old black woman with multiple sclerosis who had severe periphlebitis, peripheral retinal ischemia, and focal preretinal neovascularization in both eyes. Other causes of the peripheral neovascularization, including possible hemoglobinopathies, were specifically excluded in this patient. Subsequently, in 1981, Francoz-Taillanter and Pingault[10] described a 27-year-old woman with multiple sclerosis who had a retinal detachment in the left eye secondary to proliferative retinopathy, and severe periphlebitis, peripheral retinal ischemia, and focal preretinal neovascularization in the right eye. Other causes of proliferative retinopathy were excluded in this patient. Peripheral scatter panretinal photocoagulation was used to control the proliferative neovascularization in the right eye in this patient.

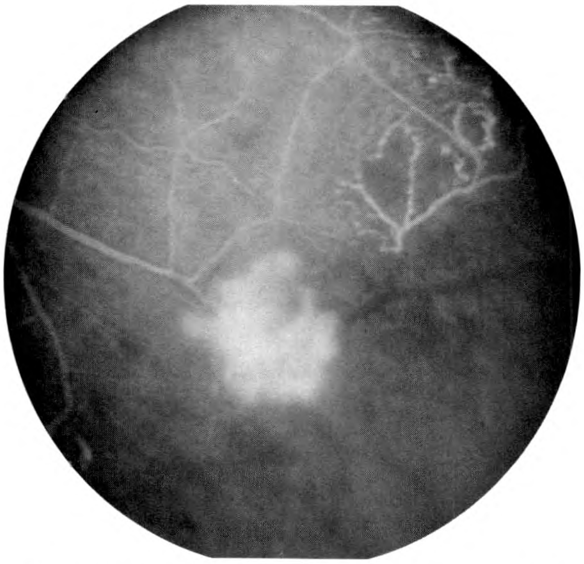

Fig. 4 (Vine). Case 2. Arteriolar venous phase of fluorescein angiogram of inferonasal peripheral retina of right eye shows frond of preretinal neovascularization located at border between vascularized and avascularized retina.

Perry and associates[11] described a 25-year-old man with acute multiple sclerosis who developed a retinal arterial occlusion in an eye with periphlebitis and severe optic neuritis, which had reduced the visual acuity to no light perception. Other causes of retinal arterial occlusion were not excluded in this report. Guigui and associates[12] also described a 40-year-old man with multiple sclerosis with diffuse periphlebitis, peripheral retinal ischemia, and focal preretinal neovascularization in each eye. Bilateral, peripheral scatter photocoagulation and a vitrectomy of one eye were required to stabilize the proliferative retinopathy in this patient. The reported laboratory examination results of this patient were limited. In all of these reports, the patients appeared to meet the criteria for multiple sclerosis but the laboratory investigation to exclude other causes of preretinal neovascularization was limited in some of these patients.

Other reports[13,14] described patients with periphlebitis, peripheral retinal neovascularization, and vitreous hemorrhage who had concurrent neurologic dysfunction, often resembling multiple sclerosis. Although these patients were described as having idiopathic preretinal neovascularization or Eales' disease with concurrent neurologic dysfunction, a review[15] of 32 patients with Eales' disease followed up from nine months to six years failed to show an association between Eales' disease and multiple sclerosis.

The patients described in this report had definite multiple sclerosis, marked periphlebitis, and peripheral retinal ischemia with focal peripheral retinal neovascularization. Other vascular and inflammatory causes[16] of peripheral retinal neovascularization were specifically excluded in these patients. A predominant feature of these two patients and previously described patients with peripheral retinal neovascularization is the presence of bilateral severe periphlebitis, which is present in a minority[6] of patients with definite multiple sclerosis. Histologic studies[6] of periphlebitis from autopsy eyes of patients with multiple sclerosis have shown that the periphlebitis consists of a segmental perivenous lymphoplasmacytic infiltrate involving anterior and posterior retinal veins. Although this vasculitis typically involves only veins, in one case[6] there was histologic evidence of a minimal periarteriolar lymphocytic infiltration. Focal periphlebitis could impede blood flow by at least three mechanisms: narrowing of the vascular lumen, damaging the nonthrombogenic nature of the vascular endothelium, and stasis. Recent studies[17] have shown that a variety of inflammatory cytokines induce endothelial cell biosynthesis and increased expression of prothrombotic activities. These combined mechanisms could induce actual thrombosis of severely inflamed retinal veins, particularly smaller peripheral veins with reduced lumina. The resulting occluded peripheral retinal capillaries would induce localized areas of ischemic retina stimulating the development of focal preretinal neovascularization, which is typically present at the border between vascularized and avascularized retina (Figs. 1 and 4).

Although both patients had peripheral retinal occlusive vasculitis, neither patient had a history or development of any other vascular thrombosis during the seven-year follow-up. The patient described in Case 1 did have a positive IgM anticardiolipin antibody, which has been associated with retinal vascular occlusions,[18] particularly in patients with systemic lupus erythematosus. Anticardiolipin antibody has been documented in a variety of neurologic diseases, and in one study,[19] 22% of patients with definite or probable multiple sclerosis had a positive anticardiolipin antibody test. The significance of a positive anticardiolipin antibody test in these neurologic diseases is uncertain. The patient described in Case 2 had bilateral peripheral retinal occlusive disease with a negative anticardiolipin antibody test and a negative lupus anticoagulant test.

The treatment of peripheral retinal neovascularization in multiple sclerosis is variable. As seen in these two patients, mild degrees of nonprogressive peripheral preretinal neovascularization without marked vitreous hemorrhage or traction do not require laser therapy and can be managed by periodic assessment. In eyes with extensive peripheral neovascularization and vitreous hemorrhage, peripheral scatter photocoagulation is usually effective in causing regression of the peripheral neovascularization. In advanced cases, secondary cicatricial changes from the peripheral retinal neovascularization can cause tractional or rhegmatogenous detachments, or both, which usually require pars plana vitrectomy techniques.

References

1. Wybar, K. C.: The ocular manifestations of disseminated sclerosis. Proc. R. Soc. Med. 45:315, 1952.

2. Lim, J. I., Tessler, H., and Goodwin, J. A.: Ante-

rior granulomatous uveitis in patients with multiple sclerosis. Ophthalmology 98:142, 1991.

3. Rucker, C. W.: Sheathing of the retinal veins in multiple sclerosis. Mayo Clin. Proc. 19:176, 1944.

4. Breger, B. C., and Leopold, I. H.: The incidence of uveitis in multiple sclerosis. Am. J. Ophthalmol. 62:540, 1966.

5. Graham, E. M., Francis, D. A., Sanders, M. D., and Rudge, P.: Ocular inflammatory changes in established multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 52:1360, 1989.

6. Arnold, A. C., Pepose, J. S., Hepler, R. S., and Foos, R. Y.: Retinal periphlebitis and retinitis in multiple sclerosis. I. Pathologic characteristics. Ophthalmology 91:255, 1984.

7. Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., Johnson, K. P., Sibley, W. A., Sieberberg, D. H., and Tourtellotte, W. W.: New diagnostic criteria for multiple sclerosis. Guidelines for research protocols. Ann. Neurol. 13:227, 1983.

8. François, M. M. P., Asseman, R., and Leroyer: Hémorrhagies récidivantes et sclérose en plaques. Bull. Mem. Soc. Fr. Ophtalmol. 73:160, 1960.

9. Morse, P. H.: Retinal venous sheathing and neovascularization in disseminated sclerosis. Ann. Ophthalmol. 7:949, 1975.

10. Francoz-Taillanter, N., and Pingault, C.: Périphlebites rétiniennes et occlusions capillaries extensives au cours d'une sclérose multiloculare. Bull. Soc. Ophtalmol. Fr. 131:699, 1981.

11. Perry, H. D., Mallen, F. J., Wright, G. D., and Maris, P. J. G.: Retinal arteriole occlusion in multiple sclerosis. Ann. Ophthalmol. 18:166, 1986.

12. Guigui, A., Brezin, A., Gaudric, A., Laroche, L., and Saraux, H.: Hémorrhagie vitreenne et proliferation neo-vasculaire au cours d'une sclérose en plaques. Bull. Soc. Ophtalmol. Fr. 139:501, 1989.

13. Singhal, B. S., and Dastur, D. K.: Eales's disease with neurological involvement. I. Clinical features in nine patients. J. Neurol. Sci. 27:313, 1976.

14. Dastur, D. K., and Singhal, B. S.: Eales' disease with neurological involvement. 2. The pathology and pathogenesis. J. Neurol. Sci. 27:323, 1976.

15. Renie, W. A., Murphy, R. P., Anderson, K. C., Lippman, S. M., McKusick, V. A., Proctor, L. R., Shimizu, H., Patz, A., and Fine, S. L.: Evaluations of patients with Eales' disease. Retina 3:243, 1983.

16. Jampol, L. M., and Goldbaum, M. H.: Peripheral proliferative retinopathies. Surv. Ophthalmol. 85:1, 1980.

17. Bevilacqua, L. P., Pober, J. S., Wheeler, M. E., Cotran, R. S., and Gimbrone, M. A.: Interleukin 1 (IL-1) activation of vascular endothelium. Effects on procoagulation activity and leukocyte adhesion. Am. J. Pathol. 121:393, 1985.

18. Levine, S. R., Crofts, J. W., Lesser, G. R., Floberg, J., and Welch, K. M. A.: Visual symptoms associated with the presence of a lupus anticoagulant. Ophthalmology 95:686, 1988.

19. Lolli, F., Mata, S., Baruffi, M. C., and Amaducci, L.: Cerebrospinal fluid anticardiolipin antibodies in neurological diseases. Clin. Immunol. Immunopathol. 59:314, 1991.

OPHTHALMIC MINIATURE

It was in his eyes that I saw the cause of her perturbation. Ordinarily gray and cold and harsh, they were now warm and soft and golden, and all adance with tiny lights that dimmed and faded, or welled up till the full orbs were flooded with a glowing radiance. Perhaps it was to this that the golden color was due; but golden his eyes were, enticing and masterful, at the same time luring and compelling, and speaking a demand and clamor of the blood which no woman, much less Maud Brewster, could understand.

Jack London, *The Sea Wolf*
New York, Bantam Books, 1986, p. 147

HLA-A29.2 Subtype Associated With Birdshot Retinochoroidopathy

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Renato Semiglia, M.D., and Jacques H. M. Cohen, M.D.

Birdshot retinochoroidopathy is strongly associated with HLA-A29. This antigen can be divided into two subtypes, A29.1 and A29.2, using an immunoprecipitation method succeeded by one-dimensional electrofocusing gel electrophoresis. We reviewed the HLA typings of 58 white French patients who had birdshot retinochoroidopathy. Of these 58 subjects, 54 (93.1%) had HLA-A29 with a relative risk of 157.30. We further analyzed the HLA-A29 subtypings of 33 patients with birdshot retinochoroidopathy. Evaluation of the results showed that HLA-A29.2 subtype was present in all patients (100%). We concluded that the absence of HLA-A29.1 subtype is statistically significant ($P < .01$) in this study of HLA-A29 subtyping.

BIRDSHOT RETINOCHOROIDOPATHY, originally described by Ryan and Maumenee[1] in 1980, is a bilateral chronic ocular entity in which the retinal autoimmunity has an important role in the manifestation of the disease.[2]

Association between birdshot retinochoroidopathy and HLA-A29 is one of the strongest HLA and disease associations and has a relative risk of 132.[2] Birdshot retinochoroidopathy is characterized by bilateral multiple cream-colored patches. These lesions are scattered throughout the fundus, grouped mostly around the optic disk.[2,3] Localization is at the level of the outer retina, pigment epithelium, and inner choroid. Although the onset and clinical appearance of the lesions vary, the depigmented spots all have a disease course of focal to widespread changes, eventually becoming confluent. Additional diagnostic criteria include vasculopathy, macular cystoid edema or simple macular edema and disk edema, or vitreitis without pars planitis with minimal inflammation of the anterior segment in an eye without external inflammation. As the disease progresses, subretinal choroidal neovascularization, optic atrophy, and preretinal membranes can be observed.

Patients and Methods

The most prominent feature of the disease is the strong association with HLA-A29.[2,4] Recent studies have shown that the serologically defined HLA-A29 can be divided into A29.1 and A29.2 subtypes, using an immunoprecipitation method succeeded by one-dimensional electrofocusing gel electrophoresis.[5] Therefore, to study the immunologic characteristics of birdshot retinochoroidopathy, we verified the initial frequency of HLA-A29 in a group of 58 patients seen in the ophthalmology department of our institution. All patients were white and included 30 women and 28 men. The mean age at which the disease manifested was 39.1 years (range, 15 to 70 years). We compared the records of this group of 58 patients to those of a control group of 443 healthy subjects in whom a retinal or choroidal disorder had been excluded. Statistical evaluation of the data included

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the determination of the relative risk factor and the use of Fisher's exact probability test.[6,7]

We further analyzed the HLA-A29 subtypes of the last 33 consecutive patients among 54 patients with HLA-A29 and birdshot retinochoroidopathy to identify a possible association with one or both of the subtypes of HLA-A29. Patients participating in this preliminary study were seen in three different departments of ophthalmology (La Pitié-Salpêtrière Hospital, University of Paris VI; Croix-Rousse Hospital, University of Lyon; and Reims Hospital, University of Reims). Human lymphocyte antigen-A29 subtyping, using an immunoprecipitation method succeeded by one-dimensional electrofocusing gel electrophoresis, was performed with minor modifications by Tabary and associates[8] in accordance with the method of Yang and associates.[9,10] This method is informative in detecting variants and subtypes of serologically defined alleles. For this study, the pooled white control group was composed of 27 healthy French subjects and 34 subjects analyzed by Yang.[9] We used Fisher's exact probability test.[6]

Results

Complete HLA-A29 typings were performed in 58 patients with birdshot retinochoroidopathy. Human lymphocyte antigen-A29 was present in 54 of the 58 patients (93.1%), whereas only 35 of the 443 healthy subjects (7.9%) shared this antigen. The relative risk factor was 157.30. Although our results differed from those of Nussenblatt and associates[2] and Priem and Oosterhuis,[3] statistical analysis of the HLA-A29 frequencies by analysis of variance confirmed the significant association with HLA-A29 ($P < .001$).

Human lymphocyte antigen-A29 subtyping determined by an immunoprecipitation method succeeded by a one-dimensional electrofocusing gel electrophoresis showed that all of the 33 patients (100%) shared the HLA-A29.2 subtype, whereas 24 of the 27 subjects in the control group (88.89%) shared this antigen. No differences in the apparent migration of the HLA-A29.2 molecules from patients and healthy subjects were observed (Figure).

Examination of the bands for HLA-A29 subtypes showed HLA-A29.2 to be a common band. The separation between HLA-A29.2 and HLA-A29.1 was marked by the basic migration of the HLA-A29.1 and pH gradient had an important role in the fine resolution of the bands.

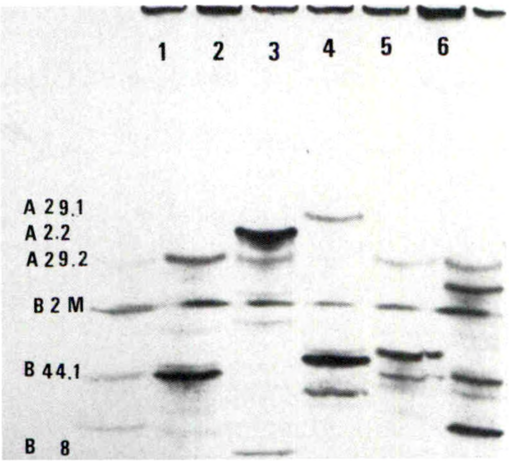

Figure (LeHoang and associates). Immunoprecipitation of HLA class-I molecules using anti-HLA class-I B9.12.1 succeeded by one-dimensional electrofocusing. Lane 1 represents a healthy subject with the HLA-A29.2 subtype; lanes 2, 3, 5, and 6 represent patients with birdshot retinochoroidopathy; and Lane 4 represents a healthy subject with the HLA-A29.1 subtype. Serologic typing was as follows: Lane 1; HLA-A1, HLA-A29, HLA-B12, and HLA-B14. Lane 2; HLA-A29 and HLA-B44. Lane 3; HLA-A2, HLA-A29, HLA-B8, and HLA-B62. Lane 4; HLA-A9, HLA-A29, HLA-B7, and HLA-B15. Lane 5; HLA-A10, HLA-A29, and HLA-B12. Lane 6; HLA-A29, HLA-B14, and HLA-B44. Human lymphocyte antigen-A29.1 and HLA-A29.2 can be discriminated easily.

Discussion

Within the terms of our study, we confirmed a strong association between birdshot retinochoroidopathy and HLA-A29. We also illustrated that all patients with birdshot retinochoroidopathy who were subjected to the protocol of HLA-A29 subtyping shared the HLA-A29.2 subtype. The considerable absence of HLA-A29.1 in 33 patients was statistically significant when compared to the pooled white control subjects ($P < .01$), using Fisher's exact probability test.

Our first consideration was the homogeneity of the patients and the control group. Our clinical experience showed that in France, the frequency of HLA-A29 varied according to the origins of the subjects. This finding correlated with the marked increase of the HLA-A29 incidence in southwestern France. Although the frequency of HLA-A29 was considerably increased in blacks, no subject had birdshot retinochoroidopathy.

The role of HLA-A29 should also be investigated. The eventual role of immune phenomena in the appearance of the disease and the mechanisms leading to the abnormal expression of the immune determinant during the course of the inflammatory reaction remain uncertain. The following hypotheses have been proposed: (1) transmission of HLA-A with the immune response genes, (2) cross reaction between the HLA-A and the responsible agent, and (3) action of HLA-A as a virus receptor.

During this immunologic response, HLA molecules control degradation, selection, and presentation of the antigens within antigen-presenting cells. The mechanism by which HLA-A29.2 confers susceptibility to birdshot retinochoroidopathy is not yet known. The presence of HLA-A29.2 subtype, either by altered antigen manifestation or by molecular mimicry, is the most probable hypothesis.[11,12] Our study provided a better understanding of the presence of HLA-A29.2 subtype in birdshot retinochoroidopathy. This finding suggested the need for prospective investigations concerning the susceptibility to birdshot retinochoroidopathy. Information obtained from this study could be used in a study designed on the basis of DNA sequence of the HLA-A29.2 molecule, as well as the immunologic basis of this disease.

References

1. Ryan, S. J., and Maumenee, A. E.: Birdshot retinochoroidopathy. Am. J. Ophthalmol. 89:31, 1980.
2. Nussenblatt, R. B., Mittal, K. K., Ryan, S., Green, W. R., and Maumenee, A. E.: Birdshot retinochoroidopathy associated with HLA-A29 antigen and immune responsiveness to retinal S-antigen. Am. J. Ophthalmol. 94:147, 1982.
3. Priem, H. A., and Oosterhuis, J. A.: Clinical manifestations in birdshot chorioretinopathy. Br. J. Ophthalmol. 72:646, 1988.
4. Priem, H. A., Kijlstra, A., Noens, L., Baarsma, G. S., De Laey, J. J., and Oosterhuis, J. A.: HLA typing in birdshot chorioretinopathy. Am. J. Ophthalmol. 105:182, 1988.
5. Yang, S. Y.: A standardized method for detection of HLA-A and HLA-B alleles by one-dimensional isoelectric focusing gel electrophoresis. In Dupont, B. (ed.): Immunobiology of HLA, vol. 1. New York, Springer Verlag, 1989, p. 332.
6. Armittage, P.: Statistical Methods in Medical Research. Oxford, England, Blackwell Scientific Publications, 1985, p. 135.
7. Schwartz, D., Lazar, P., and Papoz, L.: Statistique Medicale et Biologique, ed. 5. Paris, Flammarion Mèdicine Sciences, 1988, pp. 103–111.
8. Tabary, T., LeHoang, P., Betuel, H., Benhamou, A., Semiglia, R., Edelson, C., Cohen, J. H. M.: Susceptibility to birdshot chorioretinopathy is restricted to the HLA-A29.2 subtype. Tissue Antigens 36:177, 1990.
9. Yang, S. Y.: Population analysis of class I HLA antigens by one dimensional isoelectric focusing gel electrophoresis. Workshop summary report. In Dupont, B. (ed.): Immunobiology of HLA, vol. 1. New York, Springer Verlag, 1989, p. 309.
10. Yang, S. Y., Morishima, Y., and Collins, N. H.: Comparison of one-dimensional IEF patterns of serologically detectable HLA-A and B allotypes. Immunogenetics 19:217, 1984.
11. Tiwari, J. C., and Terasaki, P. I.: Guilt by Association. HLA and Disease Association. New York, Springer Verlag, 1989, pp. 25 and 264.
12. Benjamin, R., and Parham, P.: HLA-B 27 and ankylosing spondylitis. Immunol. Today 11:132, 1990.

Retinal Oxygenation and Laser Treatment in Patients With Diabetic Retinopathy

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The oxygen tension in the preretinal vitreous cavity was measured in human patients undergoing vitreous operations for proliferative diabetic retinopathy. The oxygen tension was significantly higher (P = .004) over areas of retina that had been treated with panretinal photocoagulation than it was over untreated areas in the same retina. This confirmed previous results in animals that showed that panretinal photocoagulation increases the inner retinal oxygen tension. We concluded that panretinal photocoagulation improves the oxygen supply to the inner retina and thereby minimizes the influence of retinal ischemia in diabetic retinopathy.

THE CONNECTION BETWEEN proliferative diabetic retinopathy and retinal oxygen metabolism was first postulated by Wise in 1956.[1] Wise suggested an association between retinal hypoxia and diabetic retinopathy. Though supported by substantial circumstantial evidence, this theory has yet to be confirmed. Further evidence of this link is laser treatment suppression of proliferative diabetic retinopathy and experimental improvement of retinal oxygenation.

Panretinal photocoagulation is a proven treatment that suppresses retinal neovascularization in diabetic retinopathy. Several experimental studies[2-6] have shown that panretinal photocoagulation increases retinal oxygen tension and counteracts retinal hypoxia. These studies have been conducted in cats, rabbits, miniature pigs, and monkeys, but have not been confirmed in humans. We examined the effect of panretinal photocoagulation on retinal oxygen tension in patients undergoing vitreous operations for complications of proliferative diabetic retinopathy.

Material and Methods

We considered patients who had already decided to undergo vitreous operations for proliferative diabetic retinopathy and its complications. They received a detailed oral and written explanation of the goals and risks of the study. We excluded those patients who were younger than 18 years old, patients in whom the fundus could not be viewed preoperatively, and patients with a blind contralateral eye. The study was reviewed and approved by the Institutional Review Board of Duke University Medical Center. Those who chose to participate signed a detailed consent form. No patient was injured in the study.

Patients who enrolled in the study were prepared routinely for vitreous operations. This preparation included obtainment of a health history, physical examination, blood tests including hemoglobin concentration, electrocardiography, and usually, thoracic radiography. General anesthesia was achieved in patients by intubation or retrobulbar local anesthesia was achieved by administration of lidocaine and bupivacaine. All patients were administered supplemental oxygen (approximately 30% oxygen) either through the endotracheal tube or though a nasal catheter with local anesthesia. The oxygen saturation of hemoglobin was measured with an oxymeter equipped with a finger clip. We attempted to maintain the hemoglobin saturation at 98% to 99%. Arterial blood pressure was measured with a cuff and auscultation, and body temperature was recorded.

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The eye was prepared routinely and a conjunctival peritectomy was created nasally and temporally to prepare for three sclerotomies. A cannula was placed in the inferotemporal sclerotomy and the irrigation fluid line was connected but not started. Sclerotomies were cut superotemporally and superonasally and cannulas were placed and plugged. A lens ring was sutured on the eye and a planoconcave contact lens was placed on the cornea. Cannula plugs were removed. The fiberoptic oxygen probe[7] was placed in the vitreous cavity through one cannula and a fiberoptic light was placed through the other cannula. The fiberoptic oxygen sensor was positioned, the fiberoptic light was dimmed maximally and pointed away from the sensor, and the oxygen tension in each spot was recorded for three to five minutes. The oxygen tension was measured in the middle of the vitreous cavity (midvitreous), and preretinally about 0.7 mm above the retina. The preretinal measurements were made over laser-treated retina and over untreated retina in the temporal part of the macula with one measurement spot about 1 disk diameter inside the laser-treated area and the other spot about 1 disk diameter outside of the laser-treated zone. The two measurement spots were within 2 to 3 disk diameters of each other in the temporal part of the posterior pole. The order in which the various spots were measured was varied at random and in some cases measurements were repeated. A total of 33 patients were involved in the study. It was not possible to perform all planned measurements in all eyes. In some eyes, blood in the vitreous body limited visibility and access to the preretinal area; in other eyes, the retina was detached or measurement areas were either fully photocoagulated or not accessible at all. For these reasons, we could only acquire paired data from eyes with photocoagulated areas and untreated areas in nine patients.

Results

Paired data were available from nine patients in whom the preretinal oxygen tension was measured over the laser-treated areas and over untreated areas of the same retina. The preretinal oxygen tension was 146 ± 59 mm Hg (mean ± one standard deviation) in the laser-treated areas and was 111 ± 55 mm Hg in the untreated areas. This difference was statistically significant according to a paired *t*-test (P = .004). The oxygen tension data from each of these eyes were analyzed and compared (Figure). All data were analyzed, including data from eyes in which it was not possible to obtain paired measurements from laser-treated and untreated retinal areas. The preretinal oxygen tension was 110 ± 42 mm Hg over untreated retinal areas in 15 eyes and was 140 ± 59 mm Hg over panretinally laser-treated areas in 12 eyes. (The values for eyes with and without laser treatment were determined on the basis of nine paired measurements and were statistically significant [P = .004] as determined by a paired Student's *t*-test.) The oxygen tension was 83 ± 37 mm Hg in the midvitreous cavity of 21 eyes. In eight eyes in which the retina was detached, the preretinal oxygen tension was 98 ± 38 mm Hg.

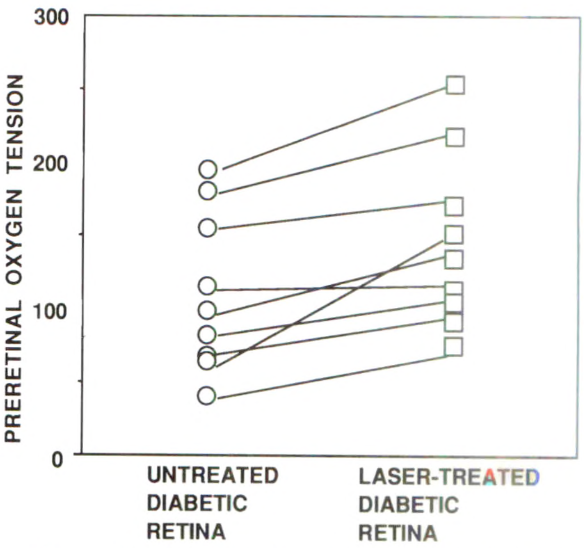

Figure (Stefánsson and associates). Preretinal oxygen tension (mm Hg) in eyes of patients with diabetes. Measurements from untreated and laser-treated areas in each eye are connected with a line. All but one of nine paired measurements showed higher oxygen tension over the laser-treated area than over the untreated area in the same eye.

Clinical data from 33 eyes were also determined (mean ± one standard deviation). The mean arterial blood pressure was 89.7 ± 13.6 mm Hg, the oxygen saturation of arterial blood hemoglobin was 98.7 ± 1.4%, and the heart rate was 76.4 ± 11.5 beats per minute. These were within narrow limits and did not seem to affect intraocular oxygen concentrations.

Discussion

This study confirmed the theory that panretinal photocoagulation increases the preretinal oxygen tension and improves the oxygenation of the retina in patients with diabetes who breathe approximately 30% oxygen. Previously, this theory has only been well supported by data from animal experiments and indirect information from human subjects. The animal experiments uniformly showed a higher oxygen tension over laser-treated retinal areas compared to the oxygen tension over untreated areas. This effect was evident at normal concentrations of ambient oxygen in rabbits[6] and miniature pigs,[4] but at high oxygen concentrations in monkeys[2] and cats.[3,5] We believe that an oxygen flux exists from the choroid through the laser scar into the inner retina in all these species. In monkeys and cats, the inner retinal circulation responds to this flux by reducing its blood flow and thereby preventing a marked change in the tissue oxygen tension.

This autoregulatory vasoconstriction is not possible in the avascular retina in rabbits.[6] Similarly, in animals breathing high concentrations of oxygen, the retinal circulation is already maximally constricted and cannot respond to the oxygen flux coming through the laser scars. Therefore, the full effect of this oxygen flux is seen in these conditions.

The patients in our study were breathing approximately 30% oxygen and their retinal oxygen tension was probably above normal and the retinal circulation was somewhat constricted. This vasoconstriction may have helped bring out the difference in oxygen tension between laser-treated areas and untreated areas, as the compensatory effect of the retinal circulation was minimized.

Maeda and associates[8] studied a similar group of patients using oxygen electrodes during vitreous operations and did not find an oxygen tension difference between laser-treated areas and untreated areas in the retinas of humans with diabetes. Their patients were breathing normal air (21% oxygen and 79% nitrogen) and retinal vasoconstriction may have countered the effect of the oxygen flux through the laser scars. Maeda's results paralleled data from normoxic cats and monkeys[2,3,5] and our results paralleled data from hyperoxic cats and monkeys[2,3,5] and normoxic rabbits and miniature pigs.[4,6] Our measurements of preretinal oxygen tension were higher than those of Maeda and associates,[8] as our patients were breathing about 30% oxygen and their patients were breathing about 21% oxygen.

The characteristics of the fiberoptic oxygen probe used in our study were discussed previously.[7] This oxygen meter has a half-response time of about 40 seconds and has to be held in place for three to five minutes to measure accurately. This limited the number of measurements made in each patient.

Wilson and associates[9] examined the retinal vessel diameters before and after panretinal photocoagulation and found retinal vasoconstriction after the laser treatment. We believe that retinal vasoconstriction is caused by the oxygen flux coming through the laser scars into the inner retina and increasing the retinal oxygen tension. Wilson and associates[9] found an association between the degree of retinal vasoconstriction and the regression of retinal neovascularization in patients with diabetes, thereby suggesting a link between the improved oxygen supply, vasoconstriction, and regression of neovascularization after panretinal photocoagulation.

References

1. Wise, G. N.: Retinal neovascularization. Trans. Am. Ophthalmol. Soc. 54:729, 1956.
2. Stefánsson, E., Landers, M. B. III, and Wolbarsht, M. L.: Increased retinal oxygen supply following panretinal photocoagulation and vitrectomy and lensectomy. Trans. Am. Ophthalmol. Soc. 79:307, 1981.
3. Stefánsson, E., Hatchell, D. L., Fisher, B. L., Sutherland, F. S., and Machemer, R.: Panretinal photocoagulation and retinal oxygenation in normal and diabetic cats. Am. J. Ophthalmol. 101:657, 1986.
4. Molnar, I., Poitry, S., Tsacopoulos, M., Gilody, N., and Leuenberger, P. M.: Effect of laser photocoagulation on oxygenation of the retina in miniature pigs. Invest. Ophthalmol. Vis. Sci. 26:1410, 1985.
5. Alder, V. A., Cringle, S. J., and Brown, M.: The effect of regional photocoagulation on vitreal oxygen tension. Invest. Ophthalmol. Vis. Sci. 28:1078, 1987.
6. Novack, R. L., Stefánsson, E., and Hatchell, D. L.: The effect of photocoagulation on the oxygenation and ultrastructure of avascular retina. Exp. Eye Res. 50:289, 1990.
7. Stefánsson, E., Peterson, J. I., and Wang, Y. H.: Intraocular oxygen tension measurements with a new fiberoptic sensor in normal and diabetic dogs. Am. J. Physiol. 256:1127, 1989.
8. Maeda, N., Tano, Y., Ikeda, T., Imai, T., Hamano, H., and Manabe, R.: Oxygen tension in the vitreous cavity of the diabetic patient. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 31.
9. Wilson, C. A., Stefánsson, E., Klombers, L., Hubbard, L. D., Kaufman, S., and Ferris, F. L.: Optic disc neovascularization and retinal vessel diameter in diabetic retinopathy. Am. J. Ophthalmol. 106:131, 1988.

Pattern Reversal Visual-evoked Response as a Prognostic Indicator in Macular Gliosis

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We recorded the preoperative pattern reversal visual-evoked responses in 16 subjects (16 eyes) with macular gliosis who underwent membrane-peeling operations. A postoperative visual improvement of one octave or more was observed in 11 of 16 eyes (68.8%). Preoperatively, ten eyes had peak amplitudes greater than or equal to 2 μV, all 11 eyes had either lowpass or bandpass curve shapes, and ten eyes had recordable responses to 20- or 10-minutes of an arc check sizes. Each of the three preoperative criteria was significantly associated with a postoperative visual improvement of one octave or more ($P = .01$, .02, and .02, respectively). These results demonstrate that the preoperative pattern reversal visual-evoked response can objectively assess the function of the underlying macula in patients with macular gliosis and, consequently, is helpful in determining which patient would most likely benefit from a membrane-peeling operation.

MACULAR GLIOSIS is characterized by the development of a preretinal membrane that often results in visual impairment. Optically, the membrane impedes normal macular function by blurring, scattering, or distorting the incident light, inducing pathologic macular changes, or a combination of these factors.

Thus, objective evaluation of the potential macular function under the membrane is useful in assessing the patient's visual prognosis, especially after surgical procedures such as membrane peeling. Preoperative visual acuity, one of numerous prognostically important preoperative factors,[1-5] is considered particularly valuable; that is, if the preoperative visual acuity is good, the postoperative visual acuity is generally good.[3,5] However, because patients for whom an operation is often indicated usually have a marked visual acuity loss, it would be worthwhile to explore whether a method exists that would assess the potential visual acuity of patients with macular gliosis, thereby reducing the reliance on preoperative visual acuity alone. We undertook this study to determine if we could objectively evaluate the macular function in cases of macular gliosis, using the steady-state pattern reversal visual-evoked response. This test was chosen as a prognostic indicator because it is known to be macular dominant.[6,7] Additionally, when optical phenomena such as distortion[8] and blurring[9] have been simulated, the alterations in the pattern reversal visual-evoked response have been studied.

Subjects and Methods

Sixteen eyes of 16 patients (eight men and eight women) with macular gliosis were chosen for this study. Eyes in which macular function could have been compromised by other factors such as notable cataractous changes were excluded. Patient ages ranged from 43 to 79 years (mean, 63.2 years). All patients were examined and operated on by either of two of us (T.H. or S.M.B.).

The pattern reversal visual-evoked response was recorded as part of the routine preoperative patient testing protocol. Steady-state pattern reversal visual-evoked responses were recorded at five different check sizes set at 160, 80, 40, 20, and 10 minutes of an arc. The pattern contrast was maintained at 30% and the check-

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erboard reversal rate was set at 12 reversals per second. Responses were collected from scalp electrodes, with the active electrode placed at Oz and referenced to Pz. The responses were filtered, with the lowpass set at 1 Hz and the highpass set at 70 Hz, amplified, averaged, and stored. An analysis time of 500 msec was used. The mean amplitude of five to six waves from 50 averaged responses obtained at each check size was calculated and plotted to obtain a pattern reversal visual-evoked response amplitude check-size function curve. Three components of the preoperative pattern reversal visual-evoked response were analyzed.

Peak pattern reversal visual-evoked response amplitudes—The peak pattern reversal visual-evoked response amplitude measurements were subdivided into the following three groups: (1) eyes with peak pattern reversal visual-evoked response amplitudes less than 2 μV (2) eyes with peak pattern reversal visual-evoked response amplitudes greater than or equal to 2 but less than 5 μV, and (3) eyes with peak pattern reversal visual-evoked response amplitudes greater than or equal to 5 μV.

Pattern reversal visual-evoked response amplitude check-size function curve—The resultant curve shapes were subdivided into the following three groups: (1) flat-shaped curves, that is, eyes with function curves in which the difference between the maximal and minimal pattern reversal visual-evoked response amplitude was less than 1 μV (Fig. 1, top left); (2) lowpass-shaped curves, that is, eyes with function curves in which the difference between the maximal and minimal pattern reversal visual-evoked response amplitude was greater than or equal to 1 μV and the function curve peaked at a check size of 160 or 80 minutes of an arc (Fig. 1, top right); and (3) bandpass-shaped curves or inverted U-shaped curves, that is, eyes with function curves in which the difference between the maximal and minimal pattern reversal visual-evoked response amplitude was greater than or equal to 1 μV and the function curve peaked at 40, 20, or 10 minutes of an arc (Fig. 1, bottom left).

Recordability of the response at 20- or 10-minutes of an arc check size—Responses to the 20- and 10-minute check sizes were analyzed and the eyes were classified as eyes that demonstrated recordable responses or eyes that demonstrated unrecordable responses. Responses were considered unrecordable if the individual response waves were unidentifiable and a fast Fourier spectrum did not show a spike at the corresponding stimulating frequency.

On the basis of the three pattern reversal visual-evoked response components, the overall preoperative pattern reversal visual-evoked response was considered good if two of the following conditions were met: (1) if peak amplitudes were greater than or equal to 2 μV, (2) if lowpass or bandpass curve shapes were present and (3) if responses were recordable at 20- or 10-minutes of an arc stimuli. All other eyes were classified as having poor pattern reversal visual-evoked responses.

Although the goal of this study was to determine the prognostic value of the pattern reversal visual-evoked response, we also documented the preoperative clinical factors that were reported to be prognostically important[1-5] to observe if they were also statistically significant in our patient population. Specifically, we studied the cause (that is, idiopathic or nonidiopathic), preoperative duration (that is, less than 12 months, between 12 and 36 months, or greater than or equal to 36 months), preoperative visual acuity (that is, less than 20/200, between 20/200 and 20/100, or 20/100 or better), membrane type (that is, thin or thick membranes, on the basis of whether the vessels under the membrane could be visualized), preoperative vitreous findings (that is, the presence or absence of vitreous traction, on the basis of biomicroscopic evidence of vitreous attachment to the membrane), and the preoperative fluorescein findings (that is, the presence or absence of leakage on fluorescein angiography).

The prognostic value of each of the pattern reversal visual-evoked responses and clinical criteria was determined by correlating them with the presence or absence of visual improvement of one octave or more after a membrane-peeling operation. Appropriate contingency tables were used. Fisher's exact test of the null hypothesis of independence was applied. A P value less than or equal to .05 indicated that the two variables of interest were related.

Results

Of the 16 eyes that were operated on, 11 (68.8%) had improvements in visual acuity of one octave or more after a membrane-peeling

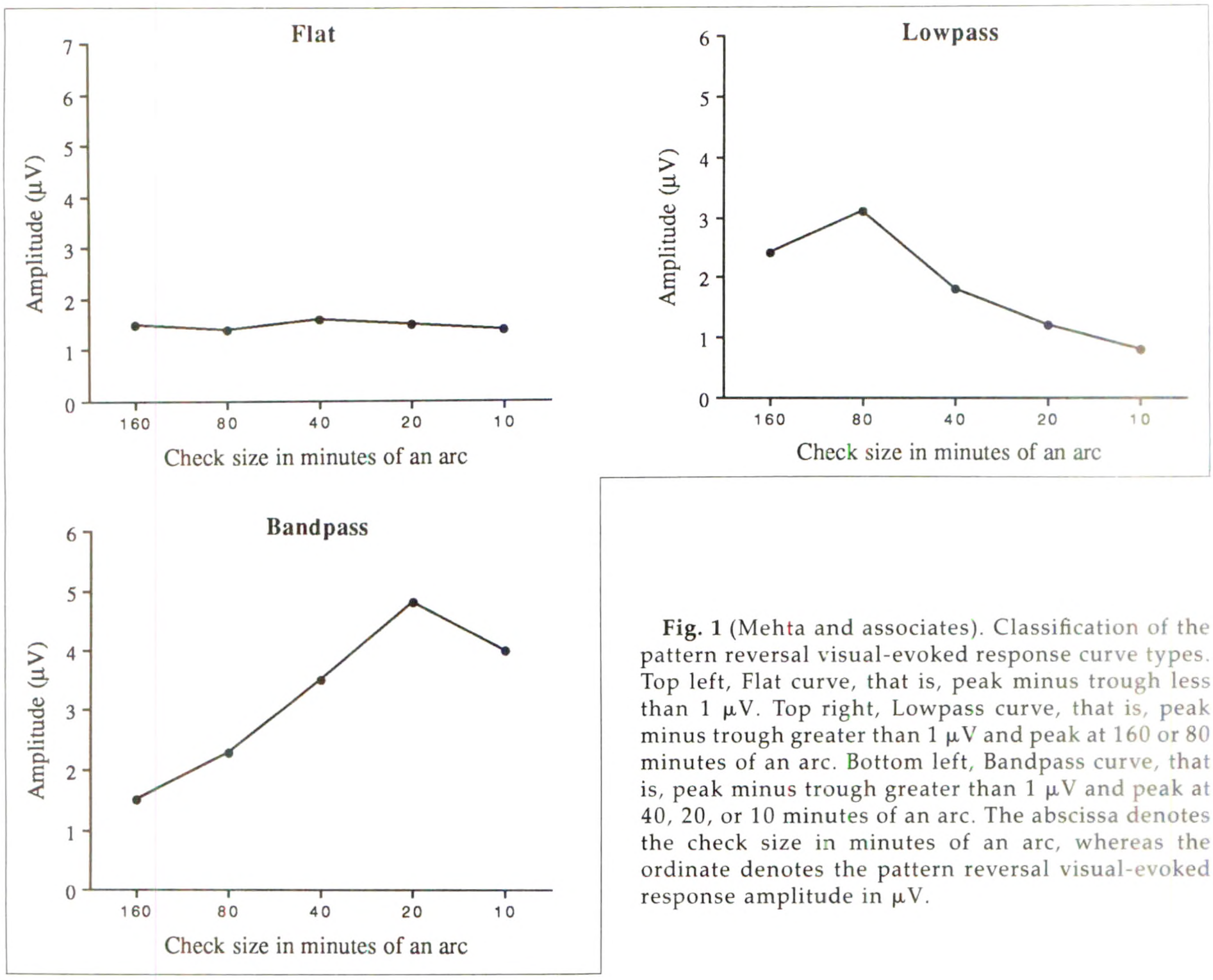

Fig. 1 (Mehta and associates). Classification of the pattern reversal visual-evoked response curve types. Top left, Flat curve, that is, peak minus trough less than 1 μV. Top right, Lowpass curve, that is, peak minus trough greater than 1 μV and peak at 160 or 80 minutes of an arc. Bottom left, Bandpass curve, that is, peak minus trough greater than 1 μV and peak at 40, 20, or 10 minutes of an arc. The abscissa denotes the check size in minutes of an arc, whereas the ordinate denotes the pattern reversal visual-evoked response amplitude in μV.

operation. The mean follow-up period was 12.8 months.

Pattern reversal visual-evoked response peak amplitudes—Of the 11 eyes that had improvement in visual acuity, ten (90.9%) had peak amplitudes greater than or equal to 2 μV. Of the five eyes that did not have improvement in visual acuity, four (80.0%) had peak amplitudes less than 2 μV. The association between the preoperative pattern reversal visual-evoked response amplitude and the presence or absence of postoperative visual improvement of one octave or more was significant (P = .01).

Pattern reversal visual-evoked response amplitude check-size function curve—The visual acuity of all six eyes (100%) that had preoperative bandpass-shaped curves improved. The visual acuity of five of the eight eyes (62.8%) with lowpass-shaped curves improved. Of the five eyes that did not improve, two (40.0%) had flat curves and three (60.0%) had lowpass-shaped curves. Interestingly, only two eyes had preoperative flat-shaped curves and the visual acuity of neither improved. The association between the preoperative pattern reversal visual-evoked response curve shape and the presence or absence of postoperative visual improvement of one octave or more was significant (P = .02).

Recordability of the response at 20- or 10-minutes of an arc check sizes—Of the 11 eyes in which visual acuity improved, ten (90.9%) had recordable responses to 20- or 10-minutes of an arc stimuli. Of the five eyes in which visual acuity did not improve, three (60.0%) had unrecordable responses to the 20- or 10-minutes of an arc stimuli. The association between the preoperative recordability of the 20- or 10-minute stimulus and the presence or absence of postoperative visual improvement of one octave or more was significant (P = .02).

Of the 11 eyes that improved, ten (90.9%) were categorized as having good preoperative pattern reversal visual-evoked responses. In contrast, of the five eyes in which visual acuity did not improve, four (80%) were categorized as having poor pattern reversal visual-evoked responses. The pattern reversal visual-evoked response type was significantly associated with the presence or absence of postoperative visual improvement of one octave or more (P = .004).

Case Report

A 41-year-old monocular man had premacular gliosis of less than six months' duration. His visual acuity had deteriorated to 20/200 and was accompanied by distortion. Clinical examination disclosed a premacular membrane (Fig. 2, left), and fluorescein angiography disclosed areas of intraretinal leakage at the macula. The pattern reversal visual-evoked response recorded at this stage demonstrated a lowpass amplitude check-size configuration with peak amplitudes greater than 5 μV (Fig. 3, plot 1). This patient was monitored closely, and three months after the first examination, the pattern reversal visual-evoked response was rerecorded. This recording was markedly different, with a smaller peak pattern reversal visual-evoked response amplitude and a lowpass amplitude check-size configuration that was beginning to flatten (Fig. 3, plot 2); the visual acuity and clinical findings had not changed. The only other notable factor was a substantial increase in the subjective distortion experienced by the patient. The patient underwent closed vitrectomy with membrane peeling. Three and one-half months after the operation, the surface of the macula was smooth with no evidence of any residual membrane or traction (Fig. 2, right) and no leak on fluorescein angiography. The pattern reversal visual-evoked response showed a bandpass amplitude check-size configuration with peak pattern reversal visual-evoked response amplitudes greater than 5 μV (Fig. 3, plot 3), together with a visual acuity of 20/20 and a disappearance of his symptoms of distortion.

The membrane type was the only one of the six preoperative clinical factors studied that was significantly associated with the presence or absence of improvement in the postoperative visual acuity by one octave or more (P = .01). The preoperative visual acuity showed only a trend rather than statistical significance (P = .09).

Discussion

Macular gliosis is often associated with some degree of visual impairment, which may or may not be reversible. Because the surgical removal of the membrane is usually successful, the postoperative visual acuity depends on the preoperative status of the macula, wherein a damaged macula substantially limits the scope of the postoperative visual improvement. To evaluate this risk, investigators have attempted to determine the pertinent prognostic criteria by statistically analyzing multiple factors. In a prospective study of 33 eyes, Trese, Chandler, and Machemer[2] concluded that eyes with transparent membranes but without cystoid macular edema were most likely to achieve good postoperative visual acuity. In a retrospective study, Rice and associates[3] identified the preoperative visual acuity and the duration of blurred vision before an operation as the two main prognostic factors. A recent report[5] identified the following significant prognostic factors in the study series: preoperative lens status, visual acuity, duration of preoperative symptoms, and intraoperative complications. Although these prognostic factors aid the clinician in evaluating the possible surgical outcome, they are subjective in nature. An objective method of assessing the underlying macular function would be of immense value as a more accurate indicator of the ultimate prognosis. Such an objective method would also help to identify preoperatively those patients with poor visual acuities who would be most likely to have a visual improvement after a technically successful operation, because the preoperative visual acuity may be poor as a result of the optical and mechanical effects of the membrane or irreversible pathologic changes in the underlying retina.

The changes in the steady-state pattern reversal visual-evoked response when the stimulus is optically altered (as would occur in eyes with gliosis) are known.[8,9] Thus, we considered the pattern reversal visual-evoked response to be ideally suited to assess the underlying retinal function objectively in macular gliosis.

The absolute pattern reversal visual-evoked response amplitudes vary considerably, yet the

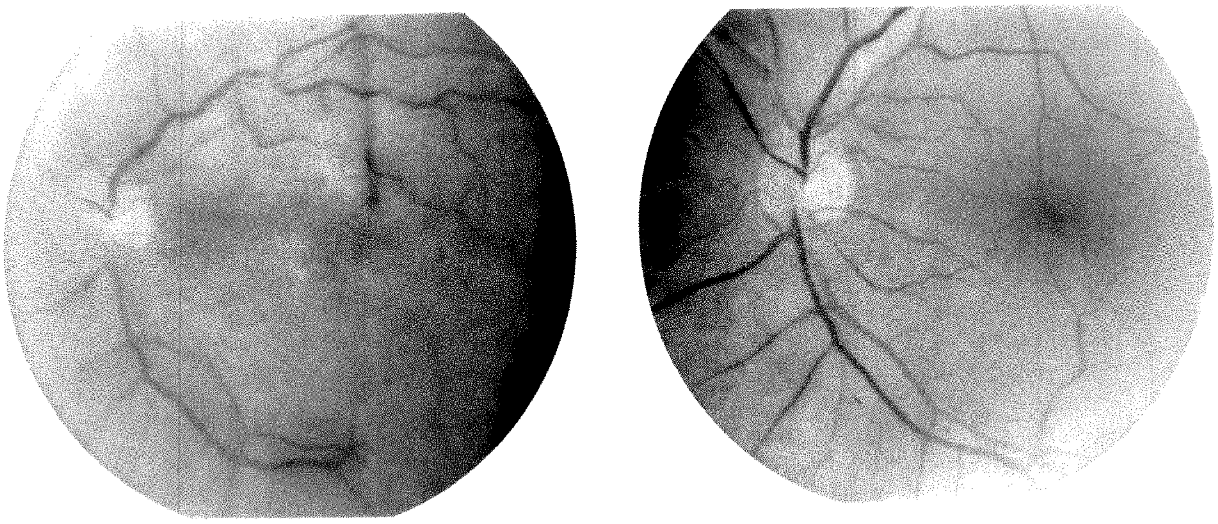

Fig. 2 (Mehta and associates). Fundus photographs from the case presented. Left, Preoperative fundus photograph three months before the operation. Right, Postoperative fundus photograph 3½ months after the operation.

overall pattern reversal visual-evoked response profile is consistent, with the responses peaking at intermediate to high spatial frequency stimuli.[6,7] Because we graphed responses from large (160 and 80 minutes), intermediate (40 minutes), and small check sizes (20 and 10 minutes), a peak response less than 2 μV, which was near noise level under our testing conditions, in eyes with otherwise clear ocular media and normal optic nerves, suggested a functional impairment of the macula.

The normal pattern reversal visual-evoked response amplitude check-size curve has a bandpass or inverted U shape. The bandpass configuration expresses the spatial frequency-tuning properties of the macula with respect to the surrounding retina.[8] Thus, the total loss of this characteristic tuning function would strongly suggest an impairment of macular function and a loss of the normal macular-extramacular relationship, indicating severe macular damage. For the curve to become flat with small peak amplitudes, the amount of optical distortion or defocusing must be marked (Tetsuka, H., Katsumi, O., Wang, G., and Morandi, A.: Presented as a poster at the Association for Research in Vision and Ophthalmology Meeting, Sarasota, Florida, May 3, 1990). Thus, flat-shaped curves coupled with low peak pattern reversal visual-evoked response amplitudes and nonrecordable responses to small check sizes suggest a degree of macular impairment that cannot be explained by optical factors alone, but one in which the degree of macular damage is also substantial. This agrees with the results of the pattern reversal visual-evoked response changes in macular holes in a study by Johnson and associates.[10]

Of the three pattern reversal visual-evoked

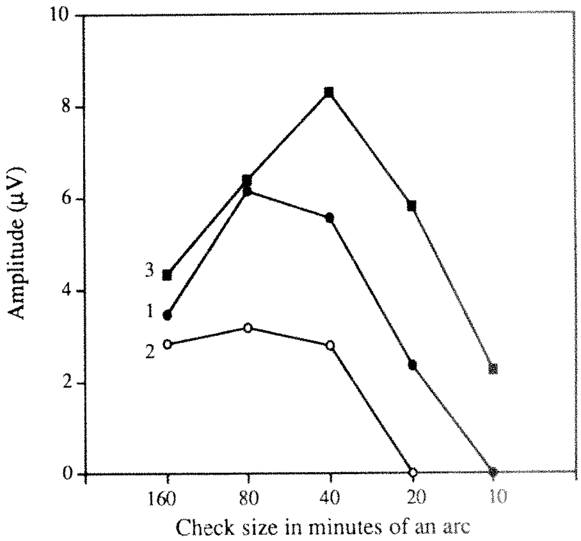

Fig. 3 (Mehta and associates). Amplitude check-size function curves from the case presented. Plots 1 and 2 indicate preoperative amplitude check-size curves recorded three months and one day before the operation. Plot 3 indicates postoperative amplitude check-size curve recorded 3½ months after the operation.

criteria we analyzed, the recordability of the 20- and 10-minute check sizes was influenced by both optical and pathologic factors. Nevertheless, if pattern reversal visual-evoked responses are recordable at these sizes, severe pathologic damage to the macula could not have occurred. This finding was evident in our results, in which ten of the 11 eyes (90.9%) that had recordable preoperative responses at these check sizes improved after a membrane-peeling operation.

Each of the three pattern reversal visual-evoked response criteria analyzed in this study reflects different aspects of macular function. Thus, combining them has greater value in judging the overall preoperative macular function. This was substantiated by our results, in which ten of the 11 eyes in which visual acuity improved (90.9%) had good pattern reversal visual-evoked responses; of the five eyes in which visual acuity did not improve, four (80%) had poor pattern reversal visual-evoked responses, although the overlying membranes had been removed completely without surgical complications.

Of the various clinical factors we studied, only the membrane type proved to be prognostically significant, a finding that agrees with that of Trese, Chandler, and Machemer.[2] Analysis of the preoperative visual acuity showed only a trend rather than statistical significance, probably because of our small sample size of 16 eyes.

The preoperative pattern reversal visual-evoked response provided us with an objective and sensitive method of evaluating and monitoring the macular function of the patient in our case report. This patient had good preoperative pattern reversal visual-evoked response criteria despite a poor visual acuity of 20/200, and achieved a final acuity of 20/20 after the operation. Although the pattern reversal visual-evoked response had changed significantly between his two preoperative visits (Fig. 3, plots 1 and 2), suggesting deteriorating macular function, his visual acuity remained unchanged, demonstrating the pattern reversal visual-evoked response's sensitivity in mirroring macular function.

References

1. Michels, R. G.: A clinical and histopathological study of epiretinal membranes affecting the macula and removed by vitreous surgery. Trans. Am. Ophthalmol. Soc. 80:580, 1982.
2. Trese, M. T., Chandler, D. B., and Machemer, R.: Macular pucker. I. Prognostic criteria. Graefes Arch. Clin. Exp. Ophthalmol. 221:12, 1983.
3. Rice, T. A., de Bustros, S., Michels, R. G., Thompson, J., Debanne, S. M., and Rowland, D. Y.: Prognostic factors in vitrectomy for epiretinal membranes of the macula. Ophthalmology 93:602, 1986.
4. de Bustros, S., Rice, T. A., Michels, R. G., Thompson, J. T., Marcus, S., and Glaser, B.: Vitrectomy for macular pucker. Use after treatment of retinal tears or retinal detachment. Arch. Ophthalmol. 106:758, 1988.
5. Pesin, S. R., Olk, J. R., Grand, G., Boniuk, I., Arribas, N., Thomas, M., Williams, D., and Burgess, D.: Vitrectomy for premacular fibroplasia. Prognostic factors, long-term follow-up, and time course of visual improvement. Ophthalmology 98:1109, 1991.
6. Regan, D., and Richards, W.: Independence of evoked potentials and apparent size. Vision Res. 11:679, 1971.
7. Regan, D.: Human Brain Electrophysiology. New York, Elsevier, 1989, pp. 390–420.
8. Mehta, M., Katsumi, O., Sakaue, H., Hirose, T., and Rosenstein, R.: Effect of artificial distortion on the pattern reversal visual evoked potential. Clin. Vis. Sci. 6:11, 1990.
9. Katsumi, O., Sakaue, H., Mehta, M. C., and Hirose, T.: Effect of optical defocus in the pattern reversal visual evoked response (PVER). Ophthalmic Res. 22:383, 1990.
10. Johnson, L. N., Yee, R. D., Helper, R. S., and Martin, D. A.: Alteration of the visual evoked potential by macular holes. Comparison with optic neuritis. Graefes Arch. Clin. Exp. Ophthalmol. 225:123, 1987.

Detection of Subretinal Neovascular Membranes With Indocyanine Green and an Infrared Scanning Laser Ophthalmoscope

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We studied 80 patients with subretinal neovascular membranes to demonstrate the features and limitations of indocyanine green angiography. Indocyanine green increased the detection of ill-defined membranes or those in larger exudative maculopathies. Each membrane had a characteristic small dark rim that demarcated it from surrounding choroidal tissue. Nevertheless, the complex vascular structures of the choroid and retina, which are displayed at one time, can sometimes render the separation of new vessels difficult when displayed at the same time. The results of our study indicate that indocyanine green angiography may be suggested as an additional diagnostic tool in cases of ill-defined or exudative subretinal neovascular membranes.

DESPITE THE USE of laser coagulation, subretinal neovascular membranes are leading causes of legal blindness in industrialized countries.[1] The Macular Photocoagulation Study established the efficacy of laser treatment for extrafoveal subretinal neovascular membranes.[2] Poorly defined subretinal neovascular membranes and eyes with pigment epithelial detachment or blood extending beneath the center of the fovea were excluded from the study.

Indocyanine green fluoresces in the near infrared light (peak absorption at 790 nm and maximal emission at 835 nm[3]) in which only 10% of the light is absorbed by the pigment epithelium. After intravenous injection, indocyanine green is rapidly and completely bound to plasma proteins in blood[4,5] and, in contrast to 10% to 30% of sodium fluorescein that remains unbound or free,[6] does not exude from fenestrated choroidal vessels. It, therefore, should be ideal for the early detection of subretinal neovascular membranes, especially for those cases that were excluded in the Macular Photocoagulation Study.

Since the propagation of indocyanine green as a fluorescent dye for retinal and later choroidal angiography,[7-9] many strategies have been developed to resolve the problem of its low fluorescence.[10] Quentel and Coscas[11] applied high doses of up to 4 mg/kg of body weight of indocyanine green, Hayashi and de Laey[12] proposed a specially designed fundus camera connecting to a video system, and Destro and Puliafito[13] combined both ideas. One of us[14] used a light-intensifying infrared charged coupled device camera mounted on a Zeiss fundus camera, thereby reducing retinal light intensities to 2 $\mu W/cm^2$. Nevertheless, none of these trials led to convincing results in the detection of subretinal membranes. All membranes were so advanced that no improved treatment could be expected.

In 1982, Mainster and associates[15] introduced scanning laser ophthalmoscopy (originally developed by Webb, Hughes, and Pomerantzeff[16]) as a technique for fundus imaging. Clinical trials with an improved instrument have shown that its image quality equals that of fundus photography. Furthermore, its unique system of laser detection allowed, for the first time, the achievement of high-quality video fluorescein angiography at low light levels.[17,18] Scheider and Schröedel,[14,19] therefore, used a modified infrared version of the scanning laser ophthalmoscope for indocyanine green angiography and achieved choroidal angiograms with high temporal and spatial resolution. In the present study, we have analyzed results with this in-

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strument in the detection of subretinal membranes.

Material and Methods

A prototype of the scanning laser ophthalmoscope (SLO 102, Rodenstock Instrumente, München, Federal Republic of Germany[20,21]) was modified for infrared angiography. Three major advantages of the scanning laser ophthalmoscope are responsible for the superior quality of infrared images. First, the system uses a horizontally and vertically deflected laser beam as a light source. The reflected light hits a sensitive detector that displays a time-resolved image on a monitor. Because only one point of the retina is illuminated and imaged at any time, scattering is avoided and thereby the contrast is enhanced. Second, the scanning laser ophthalmoscope uses inverted illumination and detection pupils. Only 1 to 2 central millimeters are used for illumination. The larger part remains for detection, which markedly increases light sensitivity. Third, because of the better infrared responsiveness of the detector, the efficacy of the scanning laser ophthalmoscope is 3.8 times better in the infrared range than in the blue range.

We used a so-called nonconfocal fundus-scanning mode with a 10-mm stop. In this mode, depth of field is large and allows the best possible visualization of all layers of the three-dimensional choroidal structure. A layer-by-layer imaging with a 1-mm stop (which comes closer to the confocal mode) is possible with infrared light, but not during indocyanine green angiography, because the amount of reflected light is markedly reduced. The scanning laser ophthalmoscope has a 780-nm laser diode built in as a light source and an 830-nm barrier filter. The maximal retinal irradiance was 1.9 $\mu W/cm^2$.

We studied the results of angiography of subretinal neovascular membranes in 80 patients. Each patient had the pupil dilated with 0.1% tropicamide. Twenty-five milligrams of indocyanine green (Cardio-Green) dissolved in 5 ml of aqueous solvent was injected into the cubital vein. Angiography was recorded on an S-VHS videotape (Panasonic AG-7500) and simultaneously digitized with a frame grabber (Image Technologies PC Vision Plus Board). The most important still frames were saved on an optical disk, and images were later photographed from a monitor (Hitachi VM-1721A). Fluorescein angiography was performed in the routine fashion; 5 ml (20%) was injected into the cubital vein and photographs were taken with a fundus camera (Zeiss FK-50) or with a second scanning laser ophthalmoscope with argon laser.

Results

The detection of subretinal neovascular membranes with indocyanine green depends mainly on the location of the vessels. The first group of patients had membranes on the pigment epithelium, which are usually detected easily with fluorescein. Subretinal neovascular vessels are detected in these patients with indocyanine green as in the early phase of fluorescein angiography just before the dye begins to leak (Figs. 1 and 2). It was easier to estimate the membrane structure and delineate its borders with indocyanine green, as the structure remained visible throughout angiography; even the resolution of small neovascular vessel loops was good (Fig. 1). A characteristic dark rim that demarcated the membrane from the surrounding choroidal tissue was also seen. A comparison of both angiographies disclosed a typical difference that was caused by the pigment epithelium's ability to absorb blue light. Although the membrane fluoresced earlier than the choroid with fluorescein, the choroid fluoresced earlier than the membrane with indocyanine green. Indocyanine green's ability to overcome the shielding effect of ocular pigments is also beneficial when centrally located membranes are partially obscured by xanthophyll, and an exact delimitation of the membrane is impossible with fluorescein (Fig. 3). This situation is complicated in this case additionally by the difficulty in determining whether the exuding areas represent one or several membranes. Both uncertainties are resolved with the use of indocyanine green, which detects membranes in large maculopathies better than fluorescein (Fig. 4). The use of indocyanine green is also beneficial in cases in which the exudation of fluorescein hampers the demonstration of a membrane. We detected a large pigment epithelial detachment with a notch with fluorescein angiography (Fig. 5). However, a possible subretinal neovascular membrane at the notch could not be clearly demarcated because of the fluorescence of the detachment. Furthermore,

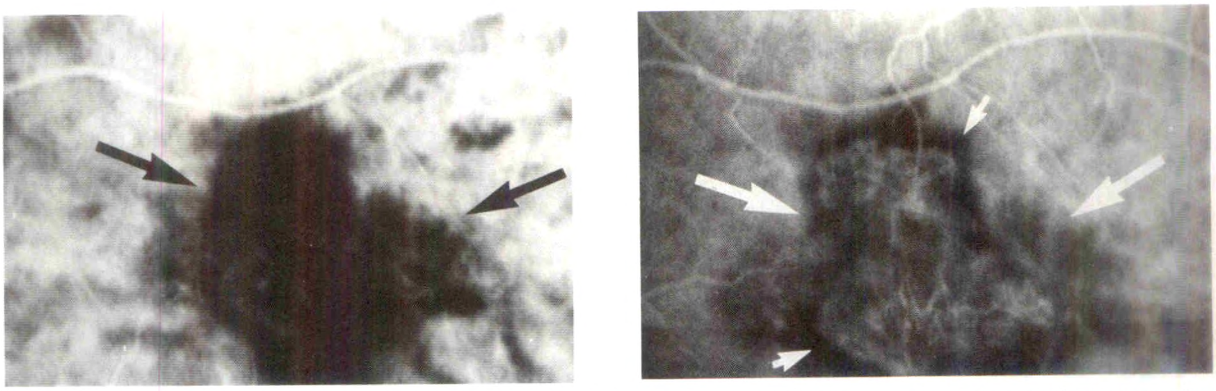

Fig. 1 (Scheider, Kaboth, and Neuhauser). Indocyanine green angiograms of a subretinal neovascular membrane that has penetrated the pigment epithelium in a 60-year-old man (long arrows). Left, Arterial and right venous phase. Right, Good resolution of even small neovascular vessel loops is demonstrated and the dark rim that demarcates the membrane from the surrounding choroidal tissue is indicated (short arrows). Note that the membrane fills later than the surrounding choroidal tissue.

the membrane seemed partially obscured by xanthophyll. In comparison, indocyanine green angiography mastered both problems and demonstrated the exact extent of the membrane (Fig. 6). Another patient provided an example of membranes that remain under the pigment epithelium. Fluorescein angiography disclosed a circumscribed area of parafoveal hyperfluorescence and scant exudation (Fig. 7). Indocyanine green angiography of this same patient disclosed a subretinal neovascular membrane under the pigment epithelium with distinct borders, thereby allowing laser coagulation (Fig. 8). The visual acuity remained at 16/20 at a one-year follow-up.

Indocyanine green's demonstrated advantage of bypassing the absorption of the pigment epithelium can be a handicap whenever the choroidal vascular net is scant (Figs. 9 and 10). In such cases it is difficult to differentiate a thin neovascular net, especially its dark rim, from regular choroidal vessels. Without fluorescein angiography, the membrane would probably not be detected. Nevertheless, the images demonstrate another minor advantage of our method. The fluorescein image is dim because of a moderate cataract; however, this is easily penetrated by the infrared light during indocyanine green angiography.

Discussion

The Macular Photocoagulation Study proved the efficacy of laser treatment. The early detection of treatable lesions is important, but is a problem in ill-defined subretinal neovascular

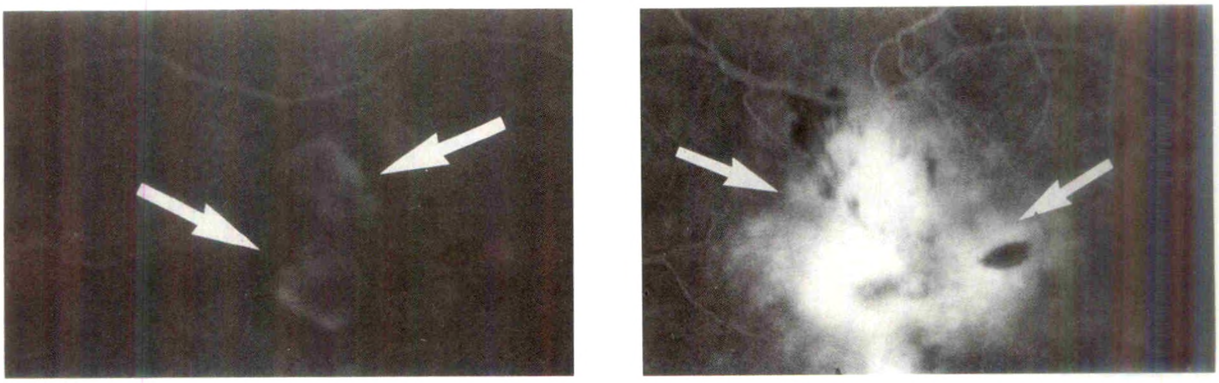

Fig. 2 (Scheider, Kaboth, and Neuhauser). Fluorescein angiograms of the same membrane as in Figure 1 (arrows). Left, Early arterial phase. Right, Midvenous phase. The demarcation of the membrane's exact borders is more difficult than with indocyanine green. In contrast to Figure 1, the membrane fluoresces earlier than does the choroid. This is caused by the absorption of blue light by the pigment epithelium.

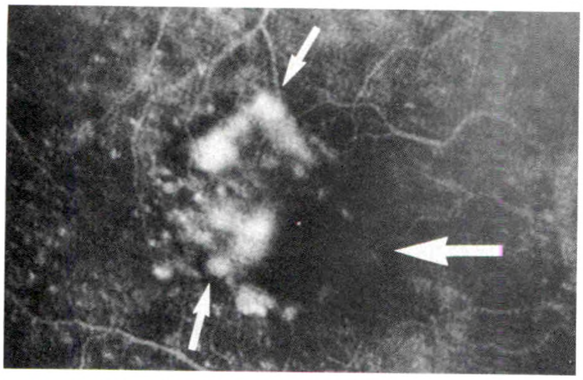

Fig. 3 (Scheider, Kaboth, and Neuhauser). Fluorescein angiogram of a subfoveal subretinal neovascular membrane in a 64-year-old man. Foveal xanthophyll (large arrow) and multiple exuding sites (small arrows) complicate the delimitation of the membrane.

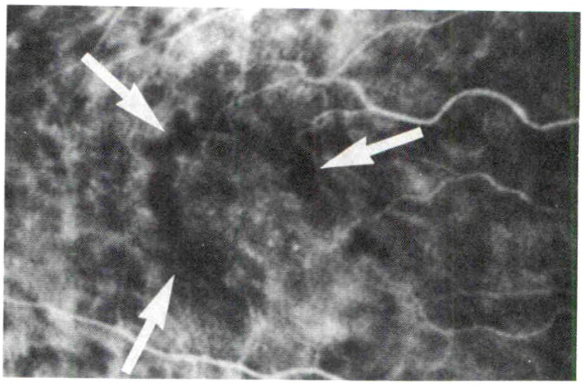

Fig. 4 (Scheider, Kaboth, and Neuhauser). Indocyanine green angiogram of the same eye as in Figure 3 that detects a large subfoveal neovascular membrane (arrows).

membranes. The characteristic properties of indocyanine green, lack of exudation and infrared fluorescence, are ideal to overcome these problems. Though resolution has improved over the years, published data do not establish definite advantages of this angiography.[12,13,22,23] Hayashi and de Laey[12] and Destro and Puliafito[13] found improved visualization of some subretinal neovascular membranes with indocyanine green angiography compared to the result achieved with conventional fluorescein angiography. However, the presented examples demonstrated far-advanced maculopathies without a chance for curative or, at least, stabilizing laser treatment. In our experience with the infrared camera, which had been used by Hayashi and de Laey[12] and Destro and Puliafito,[13] motion blur and low contrast prevented the detection of smaller membranes.[14,24] The ability to overcome the low fluorescence of indocyanine green is attributable to the infrared scanning laser ophthalmoscope. Lack of resolution is no longer an excuse for uncertain results.[19]

We studied the advantages and problems of detection of subretinal neovascular membranes with indocyanine green angiography. Our indocyanine green angiograms showed the high resolution that can now be achieved with this dye. Even the exact structure of vessel loops could be detected. Although the vessel loops can also often be seen in early phases of fluorescein angiography, a follow-up study of growth rates,[25] for example, seems to be more accurate with indocyanine green. Two of our cases involved new vessels on the pigment epithelium (Figs. 1, 2, 5, and 6). Interestingly, detection of the new vessels with indocyanine green helped us to identify the exact borders of the membrane biomicroscopically. The comparison of the indocyanine green angiographic images

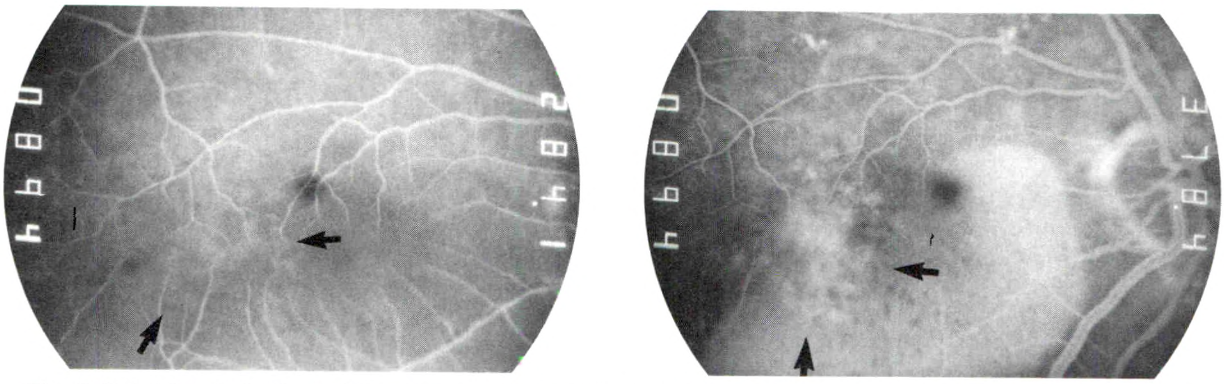

Fig. 5 (Scheider, Kaboth, and Neuhauser). Early (left) and late (right) fluorescein angiographic phases of a large pigment epithelial detachment in a 74-year-old woman. The subretinal neovascular membrane (arrows) cannot be separated clearly.

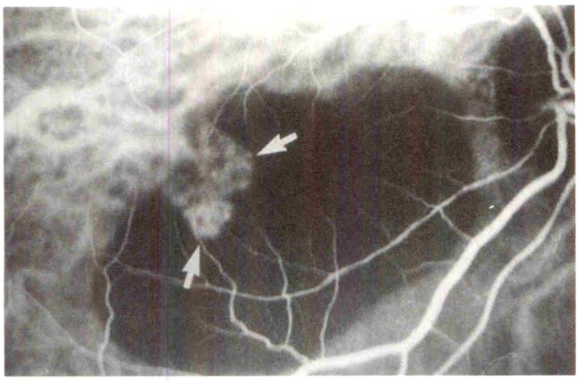

Fig. 6 (Scheider, Kaboth, and Neuhauser). Indocyanine green angiogram of the same eye as in Figure 5 disclosing a distinct neovascular net that grew on the pigment epithelial detachment (arrows).

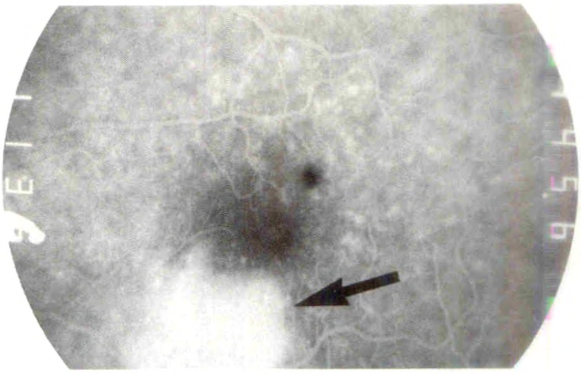

Fig. 7 (Scheider, Kaboth, and Neuhauser). Fluorescein angiogram of an ill-defined subretinal neovascular membrane with slow exudation of dye through the pigment epithelium in a 70-year-old woman (arrow).

and the biomicroscopic appearance improved our understanding of such membranes and helped during laser coagulation.

Indocyanine green does not leak regularly and this feature is most important in cases of ill-defined neovascular membranes in which exudation of fluorescein or the blockade of its fluorescence by the pigment epithelium or xanthophyll prevents diagnosis or exact localization (Figs. 3 through 8). Currently, this is the most important indication for the procedure. Indocyanine green is also suitable for real-time perfusion studies of choroidal and neovascular vessels because fluorescence is not artificially delayed by the pigment epithelium.[26] However, because the regular choroidal vessels lack blockades, separation of the vessels from neovascular membranes may be complicated. The small dark rims surrounding the subretinal neovascular membranes were helpful. These rims were certainly caused by serous fluid and did not represent an interrupted choroidal perfusion. Nevertheless, it has been demonstrated that differentiation is still not always possible. Therefore, because exudation of fluorescein remains the most important indicator of new vessels and because indocyanine green does not locate the fovea exactly (which is necessary in estimating the distance between membrane and fovea), indocyanine green angiography should always be interpreted together with fluorescein angiography.

The detection of feeding vessels was disappointing. The biggest problem remains the three-dimensional structure of the choroid, which is displayed on a two-dimensional screen. It is difficult to decide whether the vessel feeds the membrane or just passes near-

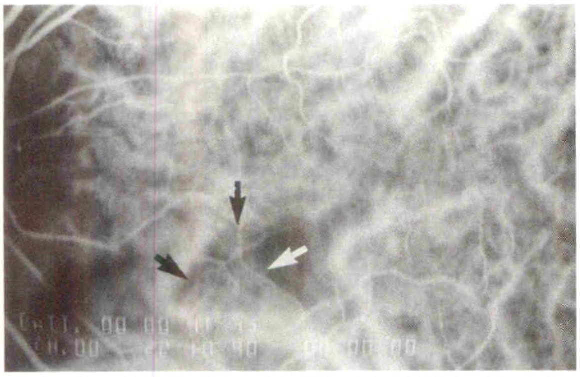

Fig. 8 (Scheider, Kaboth, and Neuhauser). Indocyanine green angiogram disclosing a neovascular net under the pigment epithelium (arrows).

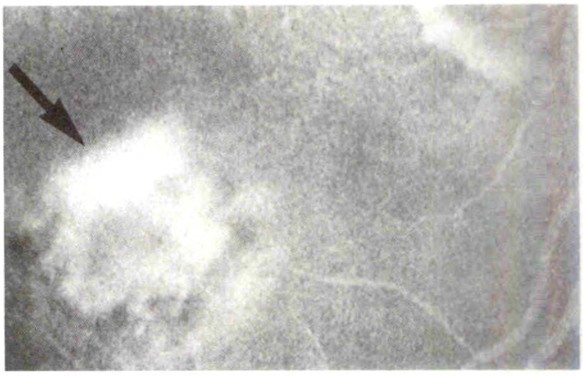

Fig. 9 (Scheider, Kaboth, and Neuhauser). Fluorescein angiogram of a parafoveal subretinal neovascular membrane in a 76-year-old man (arrow). Because of a moderate cataract, the image was rather dim.

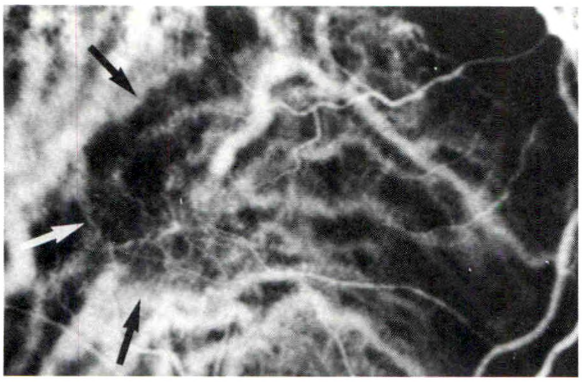

Fig. 10 (Scheider, Kaboth, and Neuhauser). Indocyanine green angiogram of the same membrane as in Figure 9. The cataract was easily overcome by the infrared light; however, because of the scant choroidal vascular net, it was difficult to separate the neovascular vessels (arrows) from the choroidal vessels.

by. First trials with stereoscopic images, recorded with the scanning laser ophthalmoscope, are promising and could overcome this problem.

No exudation of indocyanine green was found in late angiographic phases of small subretinal neovascular membranes. Earlier studies with our low-light infrared charged coupled device video system had demonstrated that this was only true for a few, mostly extensive neovascular membranes.

We are convinced that the diagnosis of subretinal neovascular membranes will improve with our procedure. Indocyanine green angiography with the infrared scanning laser ophthalmoscope increases the chance of earlier diagnosis of ill-defined subretinal neovascular membranes and is a convenient additional tool for follow-up. Further studies are needed to determine whether these new diagnostic insights will improve the long-term visual outcome after laser treatment.

References

1. Ferris, F., Fine, S. L., and Hyman, L.: Age-related macular degeneration and blindness due to neovascular maculopathy. Arch. Ophthalmol. 102:1640, 1984.
2. The Macular Photocoagulation Study Group: Argon laser photocoagulation for neovascular maculopathy. Three-year results from randomized clinical trials. Arch. Ophthalmol. 104:694, 1986.
3. Benson, R. C., and Kues, H. A.: Fluorescence properties of indocyanine green as related to angiography. Phys. Med. Biol. 23:159, 1976.
4. Cherrick, G. R., Stein, S. W., and Leevy, C. M.: Indocyanine green. Observations on its physical properties, plasma decay and hepatic extraction. J. Clin. Invest. 39:592, 1960.
5. Paumgartner, G.: The Handling of Indocyanine Green by the Liver, ed. 1. Basel, Federal Republic of Germany, Schwabe & Co., 1975, pp. 1–30.
6. Wessing, A.: Fluorescein Angiography of the Retina. Textbook and Atlas. St. Louis, C. V. Mosby, 1969, Chap. 2, p. 13.
7. Kogure, K., and Noble, D. J.: Infrared absorption angiography of the fundus circulation. Arch. Ophthalmol. 83:209, 1970.
8. Hochheimer, B. F.: Angiography of the retina with indocyanine green. Arch. Ophthalmol. 86:564, 1971.
9. Flower, R. W., and Hochheimer, B. F.: A clinical technique and apparatus for simultaneous angiography of the separate retinal and choroidal circulations. Invest. Ophthalmol. 12:248, 1973.
10. Hochheimer, B. F., and D'Anna, S. A.: Angiography with new dyes. Exp. Eye Res. 27:1, 1978.
11. Quentel, G., and Coscas, G.: Angiographie en fluorescence infrarouge au vert d'indocyanine. Bull. Soc. Ophtalmol. Fr. 84:559, 1984.
12. Hayashi, K., and de Laey, J. J.: Indocyanine green angiography of submacular choroidal vessels in the human eye. Ophthalmologica 190:20, 1985.
13. Destro, M., and Puliafito, C. A.: Indocyanine green video angiography of choroidal neovascularization. Ophthalmology 96:846, 1989.
14. Scheider, A.: Neue Verfahren zur Darstellung und Messung der Aderhautzirkulation mit Indozyanin Grün. Folia Ophthalmol. 15:283, 1990.
15. Mainster, M. A., Timberlake, G. T., Webb, R. H., and Hughes, G. W.: Scanning laser ophthalmoscopy, clinical applications. Ophthalmology 89:852, 1982.
16. Webb, R. H., Hughes, G. W., and Pomerantzeff, O.: Flying spot TV ophthalmoscope. Appl. Opt. 19:2991, 1980.
17. Nasemann, J., and Müller, M.: Scanning laser angiography. In Nasemann, J., and Burg, M. (eds.): Scanning Laser Ophthalmoscopy and Tomography. Berlin, Federal Reublic of Germany, Quintessenz Verlag, 1990, pp. 63–80.
18. Wolf, S., Toonen, H., Arend, O., Jung, F., Kaupp, A., Kiesewetter, H., Meyer-Ebrecht, D., and Reim, M.: Zur Quantifizierung der retinalen Kapillardurchblutung mit Hilfe des Scanning Laser Ophthalmoscops. Biomed. Tech. (Berlin) 35:131, 1990.
19. Scheider, A., and Schröedel, C.: High resolution indocyanine green angiography with a scanning laser ophthalmoscope. Am. J. Ophthalmol. 108:458, 1989.
20. Klingbeil, U., Plesch, A., Rappl, W., and Wutz, H.: Ophthalmic image acquisition and analysis system. In Proceedings of the International Society for Optical Engineering 1001:310, 1988.
21. Plesch, A., and Klingbeil, U.: Optical charac-

teristics of a scanning laser ophthalmoscope. In Proceedings of the International Society for Optical Engineering 1161:390, 1989.

22. Bischoff, P. M., and Flower, R. W.: Ten years experience with choroidal angiography using indocyanine green dye. A new routine examination or an epilogue? Doc. Ophthalmol. 60:235, 1985.

23. Hayashi, K., Hasegawa, Y., Tazawa, Y., and de Laey, J. J.: Clinical application of indocyanine green angiography to choroidal neovascularization. Jpn. J. Ophthalmol. 33:57, 1989.

24. Scheider, A., Korabjelnikoff, E., and Schröedel, C.: Indocyanine green angiography. First results with a scanning laser ophthalmoscope. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 462.

25. Jalkh, A. E., Nasrallah, F., Trempe, C. L., McMeel, J. W., Weiter, J. J., and Schepens, C. L.: Long-term follow-up of photocoagulated choroidal neovascular membranes in age-related macular degeneration. Ophthalmic Surg. 18:419, 1987.

26. Ben-Sira, I., and Riva, C. E.: Fluorescein angiography and ocular hemodynamics. Invest. Ophthalmol. 12:896, 1973.

Ophthalmic miniature

At the end of ten days, a new group of doctors came to Yossarian with bad news: he was in perfect health and had to get out. He was rescued in the nick of time by a patient across the aisle who began to see everything twice. Without warning, the patient sat up in bed and shouted, "I see everything twice!"

A nurse screamed and an orderly fainted. Doctors came running up from every direction with needles, lights, tubes, rubber mallets and oscillating metal tines. They rolled up complicated instruments on wheels. There was not enough of the patient to go around, and specialists pushed forward in line with raw tempers and snapped at their colleagues in front to hurry up and give somebody else a chance. A colonel with a large forehead and horn-rimmed glasses soon arrived at a diagnosis.

"It's meningitis," he called out emphatically, waving the others back. "Although Lord knows there's not the slightest reason for thinking so."

"Then why pick meningitis?" inquired a major with a suave chuckle. "Why not, let's say, acute nephritis?"

"Because I'm a meningitis man, that's why, and not an acute-nephritis man," retorted the colonel. "And I'm not going to give him up to any of you kidney birds without a struggle. I was here first."

In the end, the doctors were all in accord. They agreed they had no idea what was wrong with the soldier who saw everything twice, and they rolled him away into the room in the corridor and quarantined everyone else in the ward for fourteen days.

Joseph Heller, *Catch-22*
New York, Dell Publishing, 1955, pp. 182–183

An Atypical Fulminant Course of Choroidal Osteoma in Two Siblings

Eva Eting, M.D., and Hanna Savir, M.D.

We studied two cases of bilateral choroidal osteoma in an otherwise healthy 5-year-old boy and his only sibling, a 7-year-old sister. Both children were known to have normal fundus appearances at younger ages. The tumor showed slow growth in all four eyes, but severe visual acuity loss developed in three eyes because of neovascular complications that could not be effectively treated by photocoagulation. Secondary retinal cysts developed in three eyes.

CHOROIDAL OSTEOMA is a benign ossifying tumor of the choroid. It is typically found in healthy young females in their second or third decade, but some reported cases concern males and children younger than 10 years of age.[1,2]

The tumor is bilateral in only 25% of the cases and is usually symmetric. The main complications are the development of a subretinal neovascular membrane, subretinal fluid, and hemorrhage.[1,2] Some cases of neovascularization successfully treated by photocoagulation have been reported.[1-5] The familial development of choroidal osteomas is uncommon.[6,7]

We studied bilateral choroidal osteomas that developed in the eyes of two siblings who had normal-appearing fundi at a younger age. Subretinal neovascularization with florid expansion developed in three eyes, but was not responsive to photocoagulation.

Case Reports

Case 1

A 5-year-old boy had been treated for right-eye amblyopia since the age of 3 years in our orthoptic clinic. His medical history was unremarkable except for febrile convulsions at the age of 6 months. At that time, the fundi of both eyes had been normal in appearance. At the age of 3 years, the visual acuity was R.E.: 20/50 and L.E.: 20/30. Ocular movements and results of cover test were normal. Retinoscopy of the right eye showed plano +2.00 × 180. Retinoscopy of the left eye showed plano +1.50 × 180. Visual acuity in the right eye improved with occlusion of the left eye, but occlusion was stopped after six months because of a decrease in visual acuity in the left eye. Subsequently, visual acuity decreased again in the right eye to 20/80 and therefore, treatment was renewed at the age of 4 years. Three months later, visual acuity was 20/40 in both eyes, but had improved to 20/25 in the left eye. Eight months later, the visual acuity decreased to 20/80 in the right eye. Retinoscopy showed a white reflex and the child was referred for examination.

On initial examination, normal ocular movements in both eyes, together with normal anterior segments and clear vitreous, were observed. In the fundus of the right eye (Fig. 1), the optic disk margin was elevated on the nasal side because of the formation of a yellow-white subretinal 2-disk-diameter cyst with normal retinal vessels. At the upper and lower disk margins, yellow-white mottled subretinal lesions with scalloped geographic margins were observed. The temporal disk margin, macula, and fundus periphery were normal. The left eye (Fig. 1) had a normal disk with sharp margins. Around the nasal border of the disk, a yellow-white mottled irregular scalloped subretinal lesion and a slight elevation of the retina were

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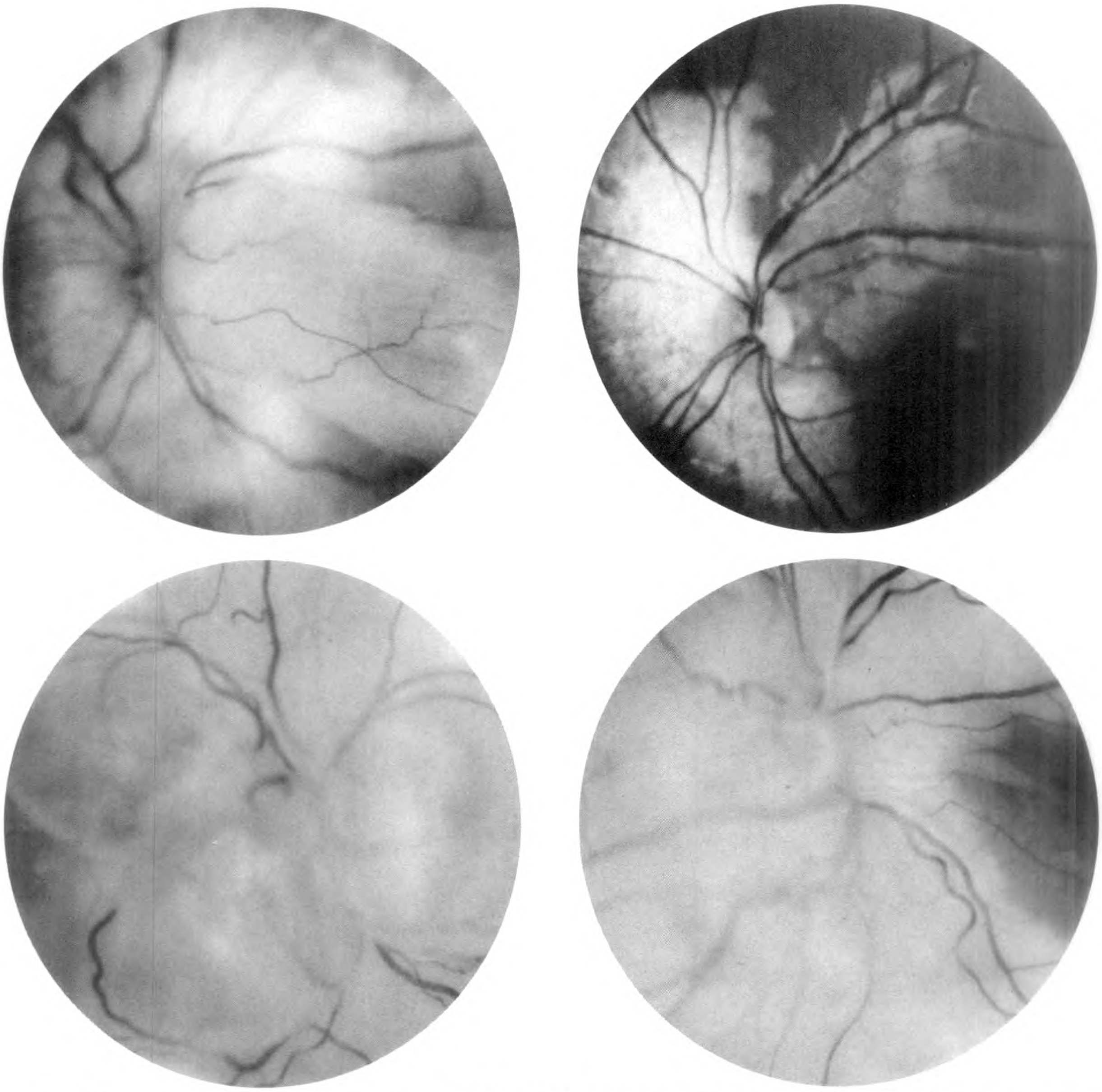

Fig. 1 (Eting and Savir). Case 1. Top row, October 1989. Top left, Right eye with elevated disk margins and cystic formation on the nasal side of the disk. Top right, Left eye with normal disk and subretinal yellow-white mottled irregular lesion. Bottom row, April 1991. Bottom left, Right eye with expanded tumor and formation of three retinal cysts around the disk. Bottom right, Left eye with secondary nasal retinal cyst and neovascular membrane encroaching the macula.

observed. Results of A- and B-scan ultrasonography were consistent with choroidal osteoma in both eyes and localized retinal detachment in the right eye. Computed tomography showed peripapillary deposits of calcium in both eyes. No history of ocular trauma or infection existed. Visual acuity in the right eye rapidly decreased to counting fingers because of expansion of the subretinal lesion that was causing detachment of the macula. Visual acuity in the left eye remained stable. But after six months, neovascularization appeared at the edge of the tumor, causing elevation of the retina on the nasal side of the disk. The left eye was treated with krypton laser photocoagulation, but neovascularization could not be stopped. Therefore, xenon-arc photocoagulation was applied to both eyes, but had no effect on the massive

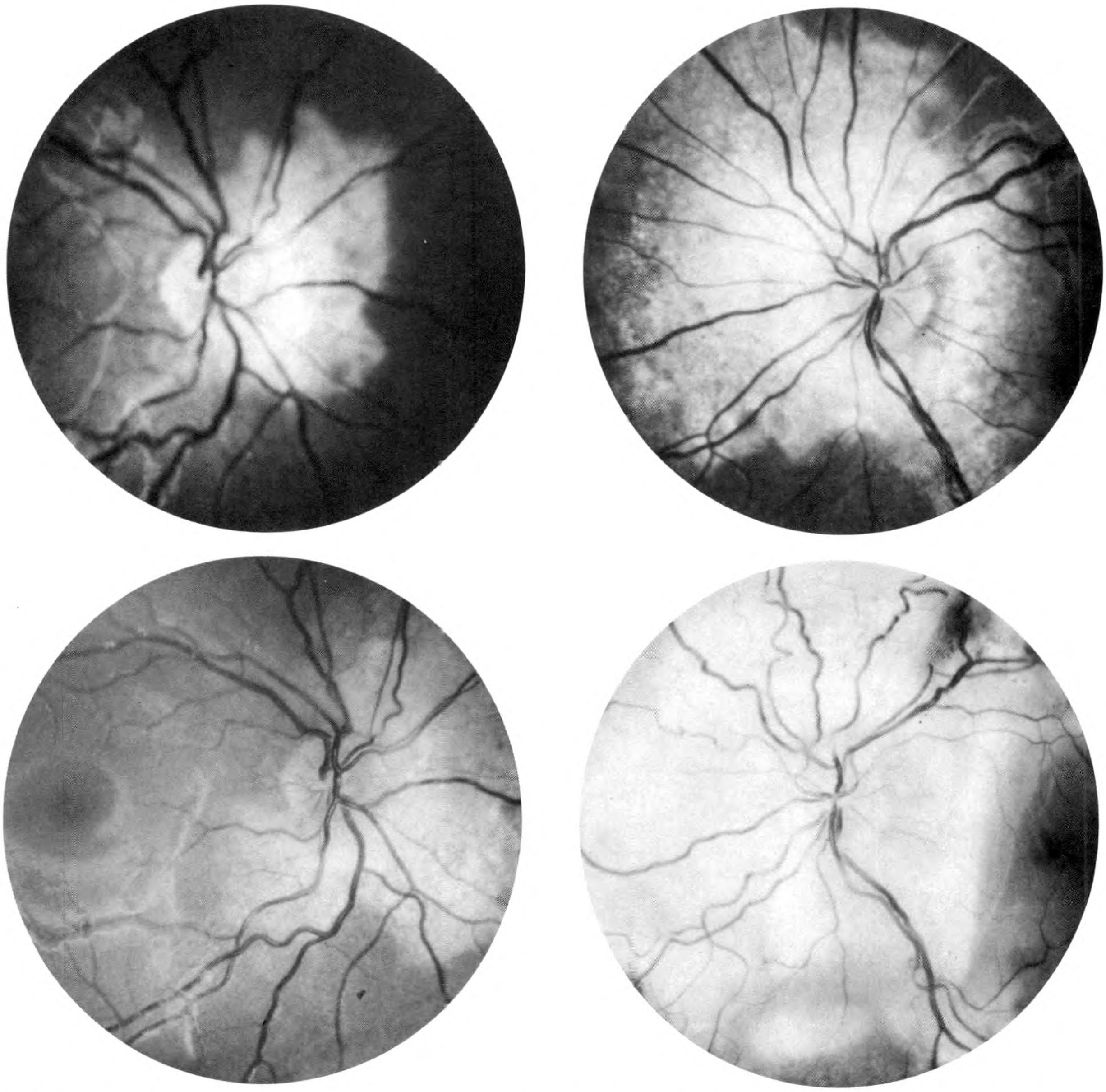

Fig. 2 (Eting and Savir). Case 2. Top row, October 1989. Top left, Right eye, and top right, left eye; both have yellow-white juxtapapillary subretinal lesions with mottled pigmentation and pseudopodium margins. Bottom row, April 1991. Bottom left, Right eye with slow lateral tumor expansion and slight retinal elevation on the nasal disk border. Bottom right, Left eye with nasal retinal cyst and shallow detachment between the disk and the macula.

neovascularization or the tumor growth. In the right eye, the tumor expanded throughout the posterior pole and three secondary retinal cysts developed around the disk (Fig. 1). Visual acuity remained counting fingers only. In the left eye, the osteoma expanded inferotemporally toward the macula, a neovascular membrane developed between the disk and the macula, and a secondary retinal cyst developed nasal to the disk (Fig. 1). Visual acuity decreased to 20/200.

Case 2

The 7-year-old sister was examined. She had no history of ocular disease or trauma. At the age of 2 years she had had normal-appearing fundi.

Examination disclosed a visual acuity of 20/

20 in both eyes. Both eyes had nasal juxtapapillary yellow-white subretinal lesions with mottled pigmentation and sharp pseudopod margins that were similar to the lesions in the boy's left eye (Fig. 2). Computed tomography showed calcium deposits in the posterior pole of both eyes. Results of ultrasonography were consistent with choroidal osteoma in both eyes. Within six months, extensive neovascular membranes developed in her left eye. Krypton laser photocoagulation was applied, but neovascularization was not stopped and the tumor spread beyond the laser-treated areas. Visual acuity decreased to 20/50 in the left eye and xenon-arc photocoagulation was added to the treatment regimen. The tumor expanded beyond the photocoagulation marks and caused retinal detachment (Fig. 2) around the disk, with the appearance of one retinal cyst and shallow retinal detachment between the disk and the macula. Tumor growth was not stopped. Visual acuity rapidly decreased to counting fingers only. The girl's visual acuity remained 20/20 in the right eye. The tumor expanded slowly, laterally, and inferotemporally toward the macula (Fig. 2). Fluorescein angiography did not show any neovascularization, but at the nasal border of the disk, slight elevation of the retina was observed.

The parents were not consanguineous. They both had visual acuities of 20/20 in both eyes and normal-appearing fundi. Chromosome study of all four family members showed no abnormalities.

Discussion

The pathogenesis and cause of choroidal osteoma are unknown. The familial development of choroidal osteomas has usually involved a mother and one or more children.[6,7] The two cases described herein involved the only two children of healthy parents. A hereditary pattern cannot be excluded and some unusual environmental influence that leads to the development of choroidal osteoma in only predisposed individuals may also exist. Both children had normal-appearing fundi at younger ages and they had no history of trauma, ocular inflammation, or systemic illness. This may indicate that the predisposition to develop choroidal osteoma is hereditary.

These siblings had a fulminant and destructive course of atypical choroidal osteoma with the severe sequelae of tumor expansion, neovascularization, retinal detachment, and the development of secondary retinal cysts in three of the four eyes at a young age, causing severe visual loss. Despite the young age of the patients, photocoagulation, first with krypton-red laser and then with xenon arc, was attempted but the destructive course could not be altered.

Most reports of successful treatment of neovascularization in choroidal osteoma concern young adults with small areas of macular or paramacular neovascularization, leading to early detection and prompt treatment. The extent and location of neovascularization in these two cases made them more difficult to treat. It is possible that the development of the retinal cysts is not caused by neovascularization, as may be indicated by the already existing elevation (Fig. 2) of the retina close to the disk in the only eye not yet showing neovascularization.

References

1. Gass, J. D. M., Guerry, R. K., Jack, R. L., and Harris, G.: Choroidal osteoma. Arch. Ophthalmol. 96:428, 1978.
2. Shields, C. L., Shields, J. A., and Augsburger, J. J.: Choroidal osteoma. Surv. Ophthalmol. 33:17, 1988.
3. Harrison, D. L., Magragal, L. E., Ehrlich, D. R., Goldberg, R. E., and Robb-Doyle, E.: Review of choroidal osteoma. Successful krypton red laser photocoagulation of an associated subretinal neovascular membrane involving the fovea. Ophthalmic Surg. 18:299, 1987.
4. Grand, M. G., Burgess, D. R., Singerman, L. J., and Ramsey, J.: Choroidal osteoma. Treatment of associated subretinal neovascular membranes. Retina 4:84, 1984.
5. Avila, M. P., El-Markabi, H., Azzolini, C., Jalka, A. E., Burns, D., and Weiter, J. J.: Bilateral choroidal osteoma with subretinal neovascularization. Ann. Ophthalmol. 16:381, 1984.
6. Cunha, S. L.: Osseous choristoma of the choroid. A familial disease. Arch. Ophthalmol. 102:1052, 1984.
7. Noble, K. G.: Bilateral choroidal osteoma in three siblings. Am. J. Ophthalmol. 109:656, 1990.

Efficacy and Safety of Nedocromil Sodium Ophthalmic Solution in the Treatment of Seasonal Allergic Conjunctivitis

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Irene Jarmoszuk, M.D., Harold Kaiser, M.D., Robert Smith, M.D.,
and Howard J. Zeitz, M.D.

To assess the efficacy and safety of twice-daily administration of nedocromil sodium 2% ophthalmic solution, we performed a multicenter study involving 140 patients with seasonal allergic conjunctivitis. Subjects had a history of seasonal allergic conjunctivitis and positive results of a skin test to ragweed. The trial coincided with the peak ragweed pollen season at five treatment centers. Patients treated with nedocromil sodium had improvements in symptoms with statistically significant reductions recorded for eye itching ($P \leq .04$), conjunctival injection ($P \leq .001$), and overall disease severity ($P \leq .001$) as compared to the placebo-treated group. Adverse events were minor and transient. We concluded that nedocromil sodium 2% ophthalmic solution administered twice daily is effective in relieving major symptoms associated with seasonal allergic conjunctivitis.

SEASONAL ALLERGIC conjunctivitis is usually a conjunctival IgE-mediated hypersensitivity reaction to the following airborne allergens: mold spores and pollens of trees, grasses, and weeds.[1] Although the pathophysiologic conditions associated with seasonal allergic conjunctivitis are not completely understood, evidence strongly suggests that it is a type I hypersensitivity response mediated by IgE antibodies bound to the membrane of mast cells in the conjunctival substantia propria.[2,3] The binding of antigen to IgE antibodies causes the release of proinflammatory mediators (for example, histamine, leukotrienes, and others). These mediators cause itching, glandular secretion, local conjunctival vasodilation, and increased vascular permeability, which in turn, cause the tearing and eyelid edema characteristic of ocular allergy.

Definitive treatment options have been scarce. Although avoidance of known allergens remains an essential approach to minimizing the discomforts of ocular allergic disease, it is difficult for patients to avoid exposure to seasonal pollens and spores without a marked impairment of the quality of life. The ability of immunotherapy to ameliorate the ocular signs and symptoms of seasonal allergy is not clearly established. Saline, vasoconstrictor, and antihistamine eyedrops are commonly prescribed for the treatment of patients with seasonal allergic conjunctivitis. Vasoconstrictors are not recommended for extended use. The use of topical corticosteroids, although clinically efficacious, is not usually appropriate in the treatment of seasonal allergic conjunctivitis because of the associated risk of cataract, glaucoma, and other unwanted side effects.

Cromolyn sodium, a carboxychromone derivative with mast-cell membrane-stabilizing properties, has been effective in the treatment of several diseases with immunologic components, including seasonal allergic conjunctivitis.[4,5] However, the dosage frequency has usually been four to six times daily. This clinical observation suggests that addressing the mast cell directly, for both prophylaxis and treatment, might have a marked therapeutic effect.[4,5]

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Nedocromil sodium is the first topically applied agent of a new class of drugs, the pyranoquinolines. It is chemically distinct from other agents currently used to treat seasonal allergic conjunctivitis including antihistamines, decongestants, anticholinergics, and cromolyn sodium. In vitro[6-8] and animal[9,10] studies have shown that nedocromil sodium inhibits several of the processes that are likely to be important in the pathogenesis of seasonal allergic conjunctivitis.[9] Specifically, nedocromil sodium inhibits human eosinophil activation,[11] mast-cell mediator release,[7,12] and antigen-induced inflammation.[13] Nedocromil sodium's inhibitory effects on these biologic processes are likely to contribute to the efficacy of this drug in the treatment of seasonal allergic conjunctivitis. Clinical studies have demonstrated the clinical efficacy and safety of nedocromil sodium especially in the treatment of patients with asthma.[14-17] The goal of our study was to evaluate the safety and efficacy of nedocromil sodium 2% ophthalmic solution administered twice daily in the treatment of seasonal allergic conjunctivitis.

Methods

Study population—One hundred fifty-five patients between the ages of 12 and 62 years were screened at five centers, and 140 were entered into the study (Table 1). Sixty-nine patients were assigned to the nedocromil sodium treatment group and 71 patients were assigned to the placebo treatment group. Of the 140 patients who entered the study, 132 completed the study (63 in the nedocromil sodium treatment group and 69 in the placebo treatment group).

All subjects had a history of seasonal allergic conjunctivitis requiring continuous treatment during the two previous pollen seasons and had a skin-test reaction of at least 2+ to ragweed. Patients with documented seasonal sensitivity to ragweed pollen were treated with a stable regimen of immunotherapy for at least three months before and during the study. Patients were excluded from the study if they met any of the following criteria: childbearing age and not using contraception, absent or minimal symptoms during the previous ragweed pollen season, no requirement for medication to control seasonal allergic conjunctivitis, evidence of perennial allergic conjunctivitis rather than seasonal allergic conjunctivitis, and clinical signs and symptoms suggesting ocular disease other than seasonal allergic conjunctivitis.

The protocol and informed-consent forms were approved by the institutional review boards in each participating medical center. Written consent was obtained from all participants.

Study sites—The study was conducted for eight weeks. The start of the double-masked portion was timed to coincide with the predicted peak of the ragweed pollen season in each of the regions where the study centers were located (approximately middle August). Two of the five sites participating in this multicenter study were located in Minneapolis, Minnesota. The other three were located in Prairie Village, Kansas; Iowa City, Iowa; and Chicago, Illinois.

Study design—The study was designed as a multicenter, double-masked, group-comparative, placebo-controlled trial of eight weeks' duration in which patients were randomly assigned to treatment. Patients were screened for entry into the program before the baseline period. At the screening visit, a complete medical history was obtained, and blood and urine samples were taken for urinalysis and routine hematologic and biochemical tests. The baseline period was initiated with the first clinic visit, during which the status of the patient's conjunctivitis was assessed and a slit-lamp examination was performed. Patients also were given daily-symptom diary cards and instructions on how to record their symptoms. After a one-week baseline period, patients were randomly assigned to either the nedocromil sodium treatment group or to the placebo treatment group. In both groups, the treatment dose was one drop (0.04 ml) of solution per eye twice daily (8:00 A.M. and 6:00 P.M.). The composition of the active drug was as follows: nedocromil sodium 2%, benzalkonium chloride 0.01%, edetate disodium 0.05%, sodium chloride 0.55%, and sufficient purified water to constitute 100%. The composition of the placebo was the same as that of the active drug, excluding the nedocromil sodium and including a nonirritating yellow coloring agent (riboflavin 0.0005%) to make the placebo visually indistinguishable from the active drug. The clinical status of the patients and the diary cards were reviewed at the end of the baseline period and at clinic visits after one, three, five, and eight weeks.

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH SEASONAL ALLERGIC CONJUNCTIVITIS

	NEDOCROMIL SODIUM-TREATED PATIENTS (N = 69)	PLACEBO-TREATED PATIENTS (N = 71)
	NO. (%)	NO. (%)
Males	35 (51)	41 (58)
Females	34 (49)	30 (42)
Mean age	32.4 years	32.2 years
(range)	(12–62 years)	(14–58 years)
Mean No. of years of conjunctivitis history	17.7	19.3
(range)	(3–56)	(3–45)
Immunotherapy-treated patients	5 (7)	2 (3)

Concomitant treatment—Other than the nedocromil sodium, no medications were permitted for treatment of ocular allergy. Orally and topically administered ocular corticosteroid preparations were not permitted for two weeks before the start of the study. Any treatment that required the use of corticosteroids during the trial was considered a failure. Rhinitis medications (nasally administered cromolyn sodium, orally administered antihistamines, orally administered decongestants, a combination of these products, and topically applied vasoconstrictors) were not permitted during the study. Orally administered theophylline and inhalation of cromolyn sodium for the treatment of asthma were not permitted during the study period. Inhaled and orally administered B-adrenergic agents and inhaled corticosteroids were permitted for asthma management as necessary, and the dosage of these drugs was recorded on a daily basis.

Artificial tears (Lyteers, Sola/Barns-Hind, Sunnyvale, California) and nasally administered corticosteroid medication (Nasalide, Syntex Laboratories, Palo Alto, California) were permitted during the study. Measured amounts of each were provided, and consumption was monitored by weighing the medicine container at each patient visit.

Symptom diary cards and clinical evaluation—The primary outcome measure was the symptom summary score, defined as the sum of scores for itchy eyes and overall eye condition. Overall eye condition included patient evaluations of burning, tearing, redness, swelling, as well as grittiness and photophobia. Patients rated eye itching, and overall eye condition on the basis of the following scale: 0 = none, symptoms absent; 1 = mild, symptoms barely noticeable; 2 = moderate, symptoms caused some discomfort; 3 = moderately severe, symptoms caused much discomfort without interfering with daily routine; and 4 = severe, symptoms present for most of the day and caused enough discomfort to interfere with daily routine. Patients also recorded the use of the study drug, use of concomitant medications, and the number of hours spent in air-conditioned rooms.

At each study visit, the examining physician evaluated the clinical status of each patient on a five-point scale (0 = none to 4 = severe) for conjunctival edema, conjunctival injection, tearing, and overall severity of conjunctivitis. Additionally, at the first and last visit, each patient underwent a thorough ophthalmic examination that was performed by an ophthalmologist and included obtainment of an ocular history, a visual acuity test, determination of intraocular pressure, physical examination of the eye and the ocular adnexa, and slit-lamp examination.

Pollen counts—Daily ragweed pollen counts were recorded at each study site using a Rotorod sampler set (Tad Brown Associates, Los Altos Hills, California) to sample one minute every ten minutes. Rods were changed every 24 hours to obtain daily counts. To ensure uniform reporting from all sites, the exposed rods were mailed to a central laboratory where the pollen counts were performed.

Data analysis—Because the study was conducted at several sites that were separated geographically and had variations in weed blooms and pollen production, it was necessary to account for regional differences in ragweed pollen counts in the data collection and analysis. Daily ragweed pollen counts were used only as an indicator of the three-week period of maximal possible ragweed pollen challenge.

To permit accurate pooling of data across the five medical centers participating in this study, a difference score was computed for each patient. The difference score was defined as the difference in diary card scores and clinical evaluation scores between the peak pollen season and the baseline period. Data for different visits thus could be pooled for different clinics, depending on the time of the peak pollen season in each region.

The composition of the two treatment groups was assessed for comparability before the trial, and the responses were evaluated during the trial both within and across clinics. The statistical significance of dichotomous variables was measured by Fisher's exact test and the Mantel-Haenszel test.[18] Quantitative or semiquantitative data were evaluated by two-sample *t*-tests and two-way analysis of variance. A P value of .05 (two-tailed test) was considered the upper limit of statistical significance.

The justification for pooling data from five centers was analyzed by testing for significant clinic by treatment interactions by means of a two-way analysis of covariance. None of the tests for clinic by treatment interactions approached statistical significance; thus, pooling data across the five clinics was statistically justified.

Adverse experiences—All adverse experiences, whether or not ascribed to the drug, were documented.

Results

Patients—The demographic characteristics of the 140 patients were analyzed (Table 1). No statistically significant differences were observed between the treatment groups with regard to age, gender, conjunctivitis history, or history of immunotherapy.

Compliance with the study treatment was good. Of the 140 patients who entered the study, eight patients withdrew from the study after starting test medication. Reasons for withdrawal included the following: protocol violation (one placebo-treated patient), other illness (four nedocromil sodium–treated patients), noncompliance (one nedocromil sodium–treated patient), treatment failure (one placebo-treated patient), and loss to follow-up (one nedocromil sodium–treated patient).

Local pollen counts at participating study sites—The ragweed pollen season began before or during the baseline period at each study site. The peak pollen season coincided with the first three weeks of the double-masked treatment segment of the study for all participating medical centers (Fig. 1). The pollen count was highest in Prairie Village, Kansas; and was decreasingly lower in Iowa City, Iowa; Minneapolis, Minnesota; and Chicago, Illinois, respectively.

Daily diary card scores—During the baseline period, all patients experienced symptoms of ocular allergy that coincided with increasing pollen counts. As compared to the symptom status of placebo-treated control patients, patients treated with nedocromil sodium during the peak pollen period had improvements in ocular symptoms usually associated with seasonal allergic conjunctivitis. This was evidenced by lower symptom scores after the initiation of treatment despite increasing pollen counts. During the three-week peak pollen period, patients treated with nedocromil sodium had lower symptom scores for itchy eyes, overall eye condition, and hence, the symptom summary score (Fig. 2). Mean individual symptom score during the peak pollen period had a statistically significant difference for eye itching ($P \leq .04$) between the placebo- and nedocromil-treated groups.

Clinical assessments—As determined by physicians, no statistically significant differences in tearing, conjunctival injection, edema, and overall severity of conjunctivitis at the end of the baseline period were found between patients subsequently assigned to either the nedocromil or placebo treatments. During the peak pollen season, patients using nedocromil sodium had statistically significant reductions in conjunctival injection ($P \leq .001$) and overall disease severity ($P \leq .001$) when compared with those of the placebo-treated group (Fig. 3). Clinical assessment of symptom scores for tearing and conjunctival edema was lower in nedocromil-treated patients, although these

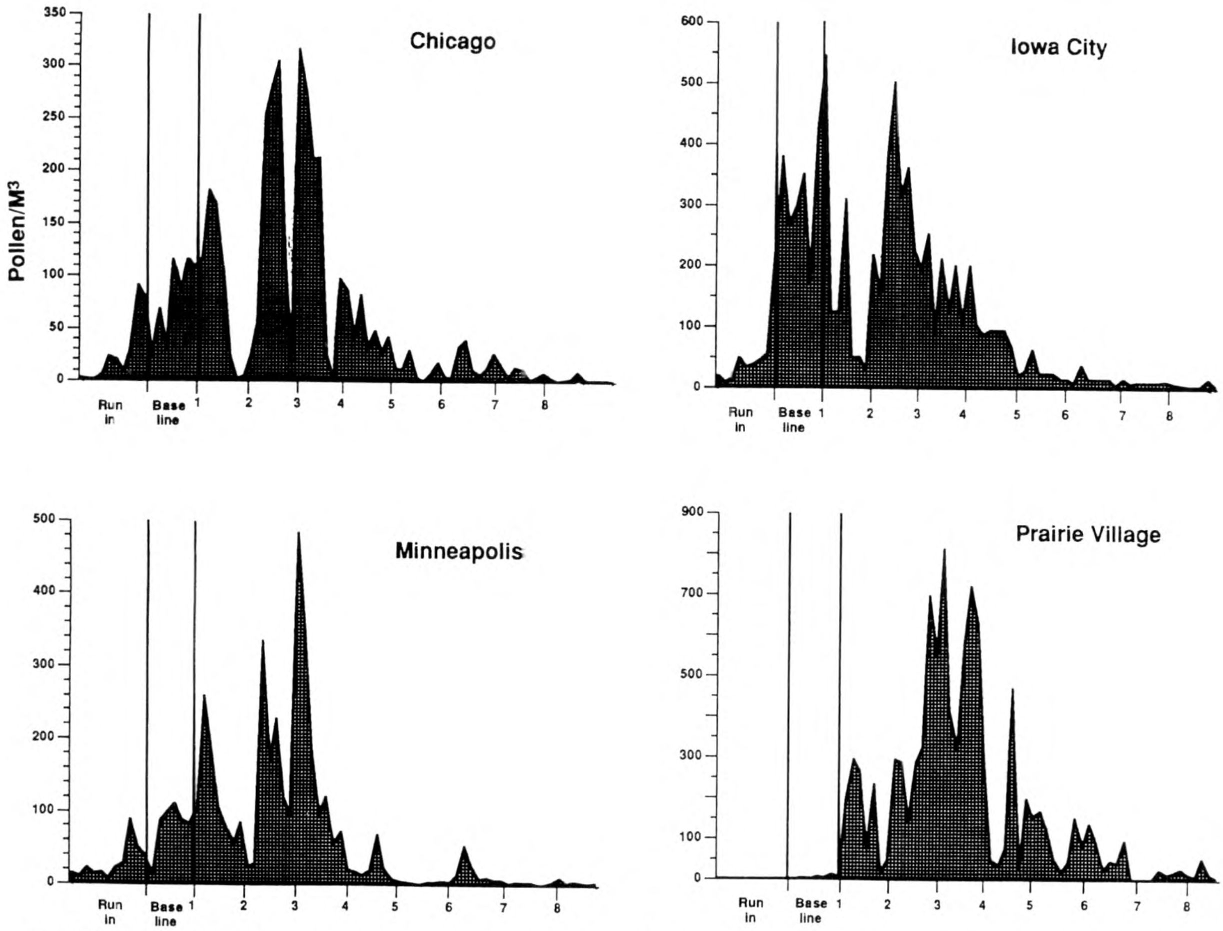

Fig. 1 (Blumenthal and associates). Ragweed pollen counts. Pollen concentration was measured at each of the four cities where the treatment centers were located. In all four cities, the ragweed pollen season began before or during the baseline period, and peak pollen season coincided with the first three weeks of the trial. Pollen count was highest in Prairie Village, Kansas.

differences failed to reach statistical significance.

Clinician and patient opinions—In evaluating the effectiveness of nedocromil sodium for allergic conjunctivitis control, clinicians rated the severity of conjunctivitis as one of the following: (1) fully controlled, (2) mostly controlled, (3) fairly controlled, (4) poorly controlled, or (5) not controlled. Of the 69 patients treated with nedocromil sodium, 38 (55%) had conjunctivitis symptoms that were at least mostly controlled. In contrast, only 23 of the 71 placebo-treated patients (32%) had similar symptom control, a difference that was statistically significant ($P \leq .004$). Likewise, 36 of the 69 patients (52%) reported that the nedocromil sodium treatment mostly controlled conjunctivitis symptoms as opposed to only 26 of the 71 (37%) placebo-treated patients ($P \leq .03$) reporting mostly controlled symptoms.

Concomitant medications—In all clinics, artificial tear use was low at baseline and during the peak pollen period. No statistically significant differences were found between treatment groups across clinics. Use of artificial tears was comparable at baseline between treatment groups (nedocromil sodium mean, 1.31 drops per day; placebo mean, 1.27 drops per day; $P \leq .78$). During the peak pollen period, the use of artificial tears was lower in the nedocromil sodium–treated group than it was in the placebo-treated group; but the difference failed to

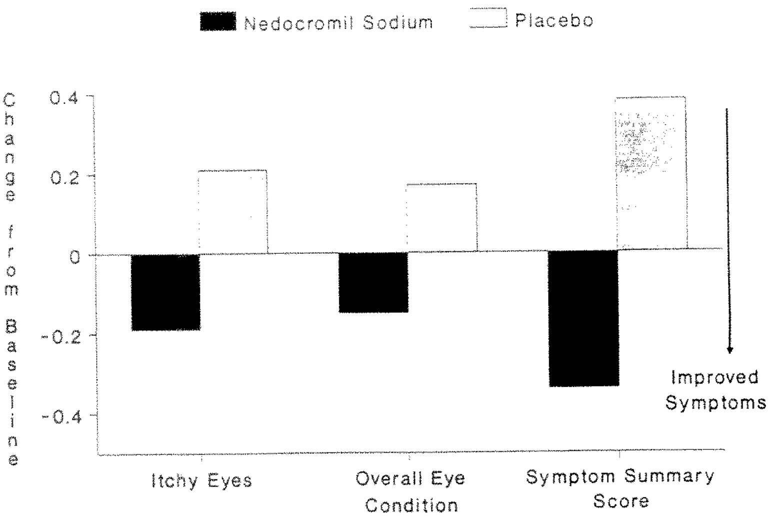

Fig. 2 (Blumenthal and associates). Daily diary score changes. During the peak pollen period, patients treated with nedocromil sodium demonstrated a statistically significant difference in eye itching (compared to the placebo-treated group, P < .04,) with improvements in overall eye condition and summary score. Values are expressed as the difference in symptom scores between the peak pollen period and baseline testing. Negative numbers, therefore, indicate an improvement in seasonal allergic conjunctivitis symptom score. In contrast, during the peak pollen season, patients treated with placebo had increases in seasonal allergic conjunctivitis symptoms.

reach statistical significance (nedocromil sodium mean, 0.45; placebo mean, 0.65; P ≤ .52). No statistically significant group differences were reported in the use of topically administered Nasalide for rhinitis during the peak pollen period.

Adverse experiences—Fifty-eight of the 71 patients in the placebo-treated group (82%) and 59 of the 69 patients in the nedocromil sodium–treated group (86%) reported at least one adverse experience during the trial. Transient burning eyes (experienced by eight [12%] of the nedocromil sodium–treated patients and by five [7%] of the placebo-treated patients), stinging eyes (experienced by seven [10%] of the nedocromil sodium–treated patients and by two [3%] of the placebo-treated patients), and unpleasant taste (experienced by nine [13%] of the nedocromil sodium–treated patients and by none [0%] of the placebo-treated patients) were the most common adverse effects associated with treatment (Table 2).

Discussion

The clinical trial was conducted during a period of maximal ragweed pollen counts. The results demonstrated the efficacy of the twice-daily administration of nedocromil sodium 2% ophthalmic solution in the treatment of season-

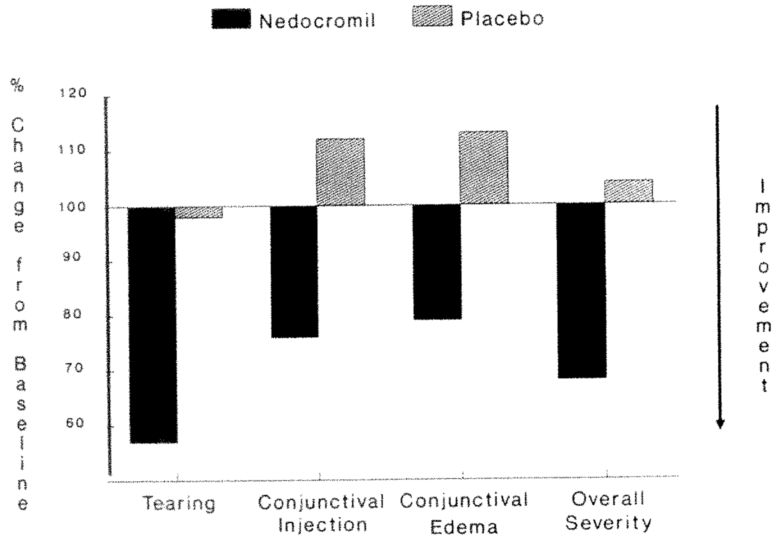

Fig. 3 (Blumenthal and associates). Clinicians' assessments of conjunctivitis. Physicians rated seasonal allergic conjunctivitis on a five-point scale (0 = absent, and 4 = severe). Numbers represent changes from baseline measures. Patients treated with nedocromil sodium had significant improvements in both conjunctival injection (P < .001) and overall severity (P < .001) when compared to patients treated with placebo.

TABLE 2
FREQUENCY OF ADVERSE CONDITIONS CONSIDERED RELATED TO NEDOCROMIL SODIUM COMPARED WITH THE FREQUENCY OF THE SAME CONDITIONS IN PLACEBO-TREATED PATIENTS

	NEDOCROMIL SODIUM-TREATED PATIENTS (N = 69)	PLACEBO-TREATED PATIENTS (N = 71)
ADVERSE CONDITION	NO. (%)	NO. (%)
Eye burning	8 (12)	5 (7)
Eye stinging	7 (10)	2 (3)
Taste perversion	9 (13)	0 (0)
Abnormal vision	1 (1)	2 (3)
Eye itching	0 (0)	2 (3)
Conjunctivitis	1 (1)	0 (0)
Eye redness	1 (1)	0 (0)
Eye irritation	0 (0)	1 (1)
Photophobia	0 (0)	1 (1)

al allergic conjunctivitis. The data supported previous studies of the efficacy of nedocromil sodium for the treatment of allergic conjunctivitis.[19,20] All treatment differences favored nedocromil sodium, with statistically significant differences noted for ocular pruritus and for the clinicians' assessments of conjunctival injection and overall severity of conjunctivitis. Opinions of treatment effectiveness expressed by both the clinician and the patient were strongly in favor of nedocromil sodium. Although the mean diary symptom summary score and overall eye condition did not reach statistical significance, trends for these symptoms also indicated a favorable response to nedocromil sodium.

The lack of statistical significance observed in several of the variables may have been caused by the treatment's initiation after the start of the pollen season when the patients were already experiencing symptoms. Optimal control of seasonal allergic conjunctivitis may be afforded by initiating treatment before the pollen season. Concomitant use of Lyteers also was lower in the placebo-treated group during the peak pollen period than during the baseline period, implying a marked placebo effect perhaps caused by the regular flushing of the eye with the eyedrop solution. This was further confirmed by the mean symptom scores that were between 1 and 2 (on the basis of a five-point scale, 0 through 4) even during peak pollen exposure.

Another factor that might have accounted for the lack of statistical significance was the fixed dosing regimen. Initial dosing four times daily may further improve the symptom control[21] in these patients. After symptoms improve, treatment may be reduced to a twice-daily regimen.[17]

Nedocromil sodium has a potentially important role in the treatment of seasonal allergic conjunctivitis. Although alternative methods are available for treatment, including saline irrigation, topically administered vasoconstrictors, topically administered antihistamines, and topically administered corticosteroids, these agents have either limited clinical efficacy or have caused unwanted side effects. The use of the mast-cell stabilizer, cromolyn sodium (4% aqueous solution) has been an effective treatment for seasonal allergic conjunctivitis when administered four times daily. Nedocromil sodium, with its broad range of anti-inflammatory activity, has been shown in vitro to be more potent than cromolyn sodium in inhibiting eosinophil activation and mast-cell mediator release, both of which are considered important in the pathogenesis of seasonal allergic conjunctivitis.[8,11,12] The results of this study showed that nedocromil is clinically effective in relieving the major symptoms of seasonal allergic conjunctivitis when administered four times daily.

When prompted, many patients in both the nedocromil sodium–treated and placebo-treated groups reported adverse experiences, but the specific complaints were usually minor. The high degree of satisfaction with the nedocromil sodium treatment and the high degree of adherence to the trial protocol demonstrated that the rate of unusual adverse experiences with the test medication did not have great clinical significance. The potential use of a drug such as nedocromil sodium, with minimal side effects and good therapeutic efficacy at twice-daily dosing, should be a beneficial addition to the clinician's armamentarium in treating patients with seasonal allergic conjunctivitis.

References

1. Allansmith, M. R., Greiner, J. V., and Ross, R. N.: Ocular allergy. In Samter, M. (ed.): Immunological Disease, ed. 4. Boston, Little, Brown, and Company, 1987, pp. 1917–1943.

2. Irani, A. M., Butrus, S. I., Tabbara, K. F., and Schwartz, L. B.: Human conjunctival mast cell. Distribution of MCT and MVTC in vernal conjunctivitis and giant papillary conjunctivitis. J. Allergy Clin. Immunol. 86:34, 1990.

3. Allansmith, M. R., and Ross, R. N.: Ocular allergy and mast cell stabilizers. Surv. Ophthalmol. 30:229, 1986.

4. Friday, G. A., Biglan, A. W., Hiles, D. A., Murphey, S. M., Miller, D. L., Rothbach, C., and Rand, S.: Treatment of ragweed allergic conjunctivitis with cromolyn sodium 4% ophthalmic solution. Am. J. Ophthalmol. 95:169, 1983.

5. Greenbaum, J., Cockcroft, D., Hargreave, F. E., and Dolovich, J.: Sodium cromoglycate in ragweed-allergic conjunctivitis. J. Allergy Clin. Immunol. 59:437, 1977.

6. Bruijnzeel, P. L. B., Warringa, R. A. J., Kok, M. L., Hamelink, M. L., and Kruekniet, J.: Inhibitory effects of nedocromil sodium on the in vitro induced migration and leukotriene formation of human granulocytes. Drugs 37(suppl. 1):9, 1989.

7. Busse, W. W., Randlev, B., Arbabian, M., and Ruoho, A.: Effect of nedocromil sodium on the B-adrenergic response of human polymorphonuclear leukocytes. Drugs 37(suppl. 1):26, 1989.

8. Enerback, L., and Bergstrom, S.: Effect of nedocromil sodium on the compound exocytosis of mast cells. Drugs 37(suppl. 1):44, 1989.

9. Abraham, W. M.: *In vitro* effects of nedocromil sodium in human and animal models. Drugs 37(suppl. 1):78, 1989.

10. Church, M. K., Hutson, P. A., and Holgate, S. T.: Effects of nedocromil sodium on early and late phase responses to allergen challenge in the guinea-pig. Drugs 37(suppl. 1):101, 1989.

11. Moqbel, R., Cromwell, O., and Kay, A. B.: The effect of nedocromil sodium on human eosinophil activation. Drugs 37(suppl. 1):19, 1989.

12. Pearce, F. L., Al-Laith, L., Bosman, J., Brostoff, J., Cunniffe, T. M., Flint, K. C., Hudspith, B. N., Jaffar, Z. H., Johnson, N. M., Kassessinoff, T. A., Lau, H. Y. A., Lee, P. Y., Leung, K. B. P., Liu, W. L., and Tainsh, K. R.: Effects of sodium cromoglycate and nedocromil sodium on histamine secretion from mast cells from various locations. Drugs 37(suppl. 1):37, 1989.

13. Dahlēn, S. E., Bjorck, T., Kumlin, M., Suabom, A., Raud, J., Palmertz, U., Franzēn, L., Gönneberg, R., and Hedquist, P.: Dual inhibitory action of nedocromil sodium on antigen-induced inflammation. Drugs 37(suppl. 1):63, 1989.

14. Lal, S., Malhotra, S., Gribben, D., and Hodder, D.: Nedocromil sodium. A new drug for the management of bronchial asthma. Thorax 39:809, 1984.

15. Eady, R. P.: The pharmacology of nedocromil sodium. Eur. J. Respir. Dis. 69(suppl. 44):112, 1986.

16. Neale, M. G., Brown, K., Foulds, R. A., Lal, S., Morris, D. A., and Thomas, D.: The pharmacokinetics of nedocromil sodium, a new drug for the treatment of reversible obstructive airways disease, in human volunteers and patients with reversible obstructive airways disease. Br. J. Clin. Pharmacol. 24:493, 1987.

17. Fairfax, A. J., and Albeson, M.: A double-blind group comparative trial of nedocromil sodium and placebo in the management of bronchial asthma. J. Int. Med. Res. 16:216, 1988.

18. Mantel, N.: Chi-square tests with one degree of freedom. Extensions of the Mantel-Haenszel procedure. J. Am. Stat. Assoc. 58:690, 1963.

19. Stockwell, A., and Easty, D.: Double-blind group comparative trial of 2% nedocromil sodium eye drops with placebo eye drops in the treatment of seasonal allergic conjunctivitis. Invest. Ophthalmol. Vis. Sci. 29:229, 1988.

20. Leino, M., Carlson, D., Jaanio, E., Koivunen, T., Lavikkala, H., Riihela, A., and Takalo, E.: Double-blind group comparative study of 2% nedocromil sodium eye drops with placebo eye drops in the treatment of seasonal allergic conjunctivitis. Ann. Allergy 64:398, 1990.

21. Bianco, S., DelBono, N., Grassi, V., and Orefice, U.: Effectiveness of nedocromil sodium versus placebo as additions to routine asthma maintenance therapy. A multicenter, double blind, group comparative trial. Respiration 56:204, 1989.

Structural and Functional Studies of the Corneal Endothelium in Diabetes Mellitus

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We performed specular microscopy, anterior segment ocular fluorophotometry, corneal pachymetry, and tonometry on 14 patients with chronic type I diabetes and nonproliferative retinopathy and on 14 age-matched control subjects. The eyes of patients with diabetes had an increased coefficient of variation of endothelial cell area, a decreased percentage of hexagonal endothelial cells, increased corneal autofluorescence, and increased intraocular pressure, which confirmed previous studies. There was no difference, however, in corneal thickness or endothelial permeability to fluorescein. Thus, we were unable to detect any abnormality in endothelial function in these diabetic corneas in the unstressed state, despite structurally abnormal endothelial cells.

AMONG THE COMPLICATIONS of diabetes mellitus, various corneal abnormalities have been observed. These include decreased sensation,[1-3] neurotrophic ulceration,[4] delayed wound healing, recurrent erosions, and epithelial edema.[5] The increased incidence of corneal complications in patients with diabetes after pars plana vitrectomy[5-7] underscores the important clinical implications of impaired corneal function, which has often been attributed to the epithelium. Although functional impairment of the diabetic corneal epithelium has been suspected,[8] Stolwijk and associates,[9] using improved methods, found no difference in epithelial permeability to fluorescein between patients with diabetes and healthy individuals. Abnormal function of the diabetic corneal endothelium has been suggested by studies of patients with diabetes showing increases in corneal thickness[10] and, after cataract extraction and vitrectomy, persistent corneal edema[7] not attributable to epithelial defects.

Structural changes in the diabetic endothelium have been observed in humans and laboratory animals. Schultz and associates[11] found structural endothelial changes in humans with diabetes, including a high coefficient of variation of cell area (polymegethism) and a decrease in the percentage of hexagonal cells (pleomorphism). Yee and associates[12] found similar changes in dogs with diabetes. Studies have shown that a polymegethous and pleomorphic corneal endothelium, despite normal cell density, is more susceptible to surgical trauma[13] and has less functional reserve.[14]

Quantitative measurement of endothelial permeability to fluorescein provides a functional assessment of the endothelial monolayer.[15] The results of Lass and associates[16] in seven subjects indicated that endothelial permeability was increased in patients with diabetes. Conversely, Watsky, McDermott, and Edelhauser[17] found no increase in endothelial permeability in six eyes of humans with diabetes in vitro. The purpose of our study was to resolve these conflicting results by quantitative measurements of corneal endothelial structure and function in a larger number of subjects with diabetes mellitus and healthy age-matched control subjects. Additionally, we sought to identify a relationship between corneal endothelial structure and function and the duration and control of the diabetes.

Material and Methods

Fourteen patients with insulin-dependent, type I diabetes and 14 healthy age-matched (±

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5 years) control subjects were recruited from Mayo Clinic employees and patients. The duration of the diabetes ranged from eight to 46 years (mean, 22 ± 11 years). The patients all had clinical histories of type I diabetes mellitus, including an abrupt onset of symptoms, propensity toward ketosis, absolute insulin deficiency, and disease onset at a young age.

All participants had clear corneas and background (nonproliferative) diabetic retinopathy. Patients with proliferative diabetic retinopathy or a history of ocular operations, photocoagulation, contact-lens use, trauma, inflammation, or glaucoma were excluded. The use of ocular medications or oral carbonic anhydrase inhibitors was not allowed within two weeks of the study.

After written informed consent was obtained, all subjects underwent a complete ocular examination including slit-lamp biomicroscopy, applanation tonometry, and ophthalmoscopy. The patients with diabetes also underwent dilated indirect ophthalmoscopy and fundus biomicroscopy. The background fluorescence (autofluorescence) of the cornea was measured with a two-dimensional scanning ocular fluorophotometer[18] before instilling fluorescein for applanation tonometry.

Specular microscopy and pachymetry were performed on both eyes of all subjects with a wide-field specular microscope. Five to ten endothelial photographs of each eye were obtained. Endothelial photographic negatives were projected at × 500 magnification, and the apices of 100 endothelial cells in each eye were digitized. An endothelial analysis system with an algorithm that assumes that the cell sides are straight lines connecting the vertices calculated the mean and standard deviation of endothelial cell size, the endothelial cell density, and the percentage of six-sided cells for each cornea. The coefficient of variation of cell size was obtained by dividing the standard deviation of cell area by mean cell area for each eye.

At 2:00 A.M. on a later day, each subject who was less than 50 years of age instilled one drop of 2% fluorescein five times, every five minutes, in both eyes and then returned to sleep. The two subjects who were more than 50 years of age (one in each group) used only three drops of 2% fluorescein because we have found that older individuals require fewer instillations than do younger individuals to obtain adequate stromal concentrations of fluorescein. Because epithelial permeability to fluorescein does not increase with age,[19] perhaps the increased penetration in older individuals is caused by their tendency not to wash away the fluorescein by reflex tearing. Residual fluorescein was removed from eyelids and eyelashes with a moist cotton ball when the subjects awoke in the morning. Fluorescein concentrations of the corneal stroma and anterior chamber of each eye were measured at 8:00 A.M., 12:00 noon, and 4:00 P.M. Three scans of each eye were performed at each measurement and the results were averaged. Endothelial permeability to fluorescein and aqueous humor flow rate were determined as described by Carlson and associates.[20] Fluorescence polarization of the cornea was measured during the scan performed at 12:00 noon.[21]

After the scan performed at 8:00 A.M., a venous blood sample was drawn from patients with diabetes for measurement of total glycosylated hemoglobin.[22] Total glycosylated hemoglobin levels approximate average blood glucose levels over two to three months and are considered relative indicators of diabetic control. The mean glycosylated hemoglobin level was 10% ± 1.4% (range, 8.2% to 12.3%). Total glycosylated hemoglobin values are interpreted in our laboratory as follows: good diabetic control = < 9%, fair control = 9% to 12%, and poor control = > 12%.

The mean of the values for the subject's right and left eyes was used for each variable for each individual. Each variable in the group with diabetes was compared with that of the control group using a double-sided Student *t*-test for sample means. Correlations between various variables were evaluated with Pearson and Spearman correlation coefficients; $P < .05$ was considered statistically significant.

Results

The duration of diabetes and the diabetic glycemic control profile were determined according to our laboratory criteria. Three subjects had good glycemic control (< 9% glycosylated hemoglobin), nine subjects had fair control (9% to 12% glycosylated hemoglobin), and two subjects had poor control (> 12% glycosylated hemoglobin), resulting in a group average of fair glycemic control over the 100 to 120 days before the determination.

The structural and functional results of patients with diabetes and control subjects were compared (Table; Figs. 1 through 5). Differenc-

TABLE

MEASUREMENTS OF STRUCTURE AND FUNCTION OF CORNEAL ENDOTHELIUM IN 14 PATIENTS WITH DIABETES AND 14 CONTROL SUBJECTS

	PATIENTS WITH DIABETES (MEAN ± SD) (N = 14)	CONTROL SUBJECTS (MEAN ± SD) (N = 14)	P VALUE*
Age (yrs)	33 ± 12	33 ± 10	.86
Endothelial permeability to fluorescein ($\times 10^{-4}$ cm/min)	4.58 ± 0.68	4.76 ± 0.71	.52
Corneal thickness (mm)	0.56 ± 0.02	0.56 ± 0.04	.90
Mean endothelial cell area (μm^2)	350 ± 35	328 ± 60	.24
Endothelial cell density (cells/mm^2)	2883 ± 280	3131 ± 483	.11
Coefficient of variation of cell area	0.29 ± 0.05	0.25 ± 0.04	.02
Hexagonal cells (%)	68 ± 8	74 ± 8	.05
Initial stromal fluorescein concentration (ng/ml)	935 ± 775	927 ± 633	.98
Aqueous humor flow rate (μl/min)	2.5 ± 0.4	3.0 ± 0.9	.08
Intraocular pressure (mm Hg)	17 ± 2	14 ± 1	.002
Corneal autofluorescence† (ng/ml fluorescein equivalents)	3.8 ± 1.2	2.2 ± 0.4	.001
Corneal fluorescence polarization	0.13 ± 0.02	0.14 ± 0.02	.56
Anterior chamber fluorescence polarization	0.04 ± 0.02	0.04 ± 0.02	.62

*Two-tailed *t*-test for sample means.

†Measured in ten patients with diabetes and ten age-matched control subjects.

es between the two groups in coefficient of variation of cell area, percentage of six-sided cells, intraocular pressure, and autofluorescence of the cornea were statistically significant. Differences in age, corneal thickness, endothelial permeability to fluorescein, mean endothelial cell area, initial stromal fluorescein concentration, aqueous humor flow rate, and corneal and anterior chamber fluorescence polarization between patients with diabetes and control subjects were not statistically significant.

The autofluorescence of the cornea in patients with diabetes was significantly correlated inversely with the percentage of six-sided cells (r = −.80, P = .006). No abnormal structural or functional variable in patients with diabetes was significantly correlated with age, duration of diabetes, or glycosylated hemoglobin level.

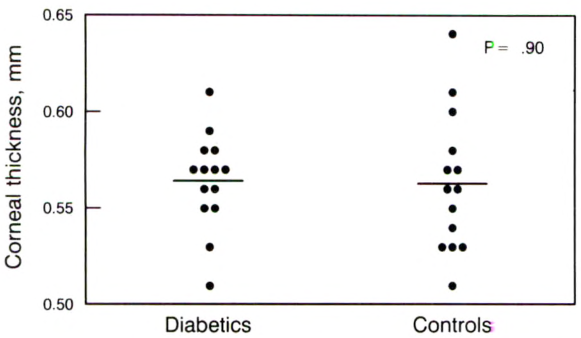

Fig. 1 (Keoleian and associates). Measurements of corneal thickness in 14 patients with diabetes and 14 healthy control subjects (bar = mean).

Discussion

We chose patients with chronic type I diabetes (range, eight to 46 years; mean, 22 ± 11 years) so the usual effects of diabetes on the

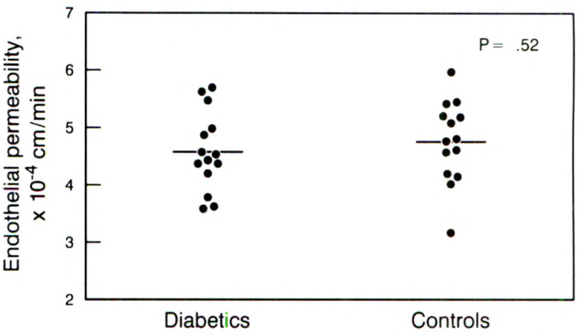

Fig. 2 (Keoleian and associates). Measurements of corneal endothelial permeability to fluorescein in 14 patients with diabetes and 14 healthy control subjects (bar = mean).

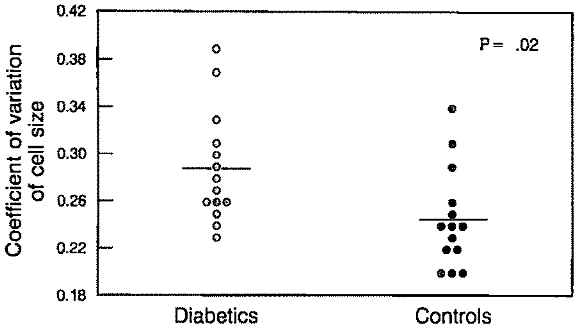

Fig. 3 (Keoleian and associates). Measurements of coefficient of variation of endothelial cell size in 14 patients with diabetes and 14 healthy control subjects (bar = mean).

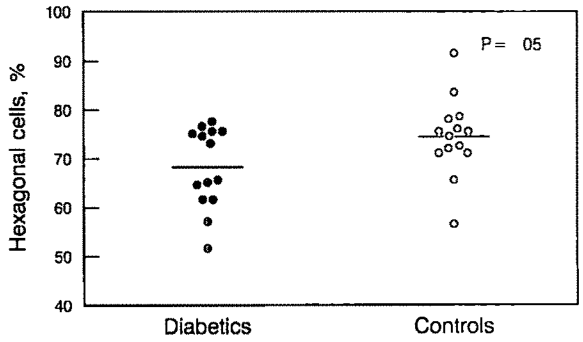

Fig. 4 (Keoleian and associates). Measurements of percentage of hexagonal cells in 14 patients with diabetes and 14 healthy control subjects (bar = mean).

anterior segment of the eye would be manifest. Both the systemic and ocular effects of diabetes increase with duration of the disease.[23-25] We did not include patients with ocular neovascularization to exclude effects secondary only to this complication or to its treatment with photocoagulation.

We found no indications of abnormal endothelial function in patients with diabetes. Corneal endothelial permeability to fluorescein was not different between patients with diabetes and control subjects. This study would detect a true increase in permeability of 0.77×10^{-4} cm/min (16%) with 90% power ($\alpha = .05$, $\beta = .10$, one-tailed).[26] We were 90% confident, therefore, that the true difference, if any, in endothelial permeability between patients with diabetes and healthy control subjects was not more than 16%. In contrast, Lass and associates[16] found a 31% increase in permeability in seven subjects with diabetes compared to control subjects. The results of Lass and associates may be explained by the maldistribution of fluorescein in the stroma that occurred in their method, as noted by Carlson and associates.[20] Our results confirmed those of Watsky, McDermott, and Edelhauser,[17] who measured endothelial permeability to carboxyfluorescein in corneas of humans with diabetes in vitro. We also found no difference in corneal thickness between patients with diabetes and control subjects. This was in contrast to the results of Olsen, Busted, and Schmitz[10] and Busted, Olsen, and Schmitz,[27] who found a small but significant increase in corneal thickness in a larger number of patients with diabetes.

Baseline corneal thickness and endothelial permeability are measurements of endothelial function in the resting state. The rate of thinning of corneas with induced swelling is a measure of endothelial functional reserve[28,29] and is abnormal in corneas of rabbits with alloxan-induced diabetes.[30] The functional reserve of corneas in humans with diabetes is also possibly depressed, despite the normal function in the unstressed resting state. A recent study by Goebbels and Spitznas[31] is consistent with this idea. These authors found a greater increase in the corneal transfer function for fluorescein after phacoemulsification in patients with diabetes than in those without diabetes. Although they did not measure endothelial permeability because they did not measure corneal thickness, the difference in transfer function that they found is best explained by greater permeability in the patients with diabetes.

Results of our study of the structure and function of the corneal endothelium in diabetes mellitus confirmed those of other investigators.[11,32,33] The diabetic endothelial cells had polymegethism, as made manifest by a larger

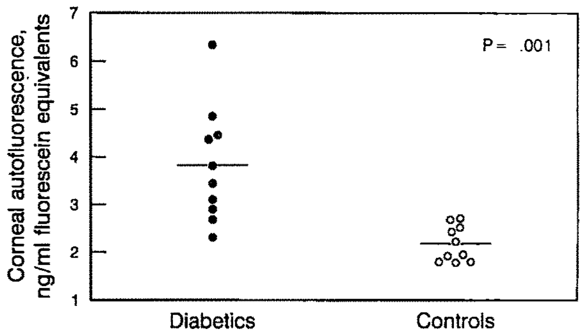

Fig. 5 (Keoleian and associates). Measurements of corneal autofluorescence in ten patients with diabetes and ten healthy control subjects (bar = mean).

coefficient of variation of cell area; and pleomorphism, as made manifest by a smaller percentage of hexagonal cells. Despite these abnormalities, the mean cell area of the corneal endothelium in patients with diabetes did not differ significantly from that of control subjects.

The factors causing structural change in the diabetic endothelium are not known, although animal studies have given insights into possible mechanisms. Matsuda and associates[34] found that rats with diabetes that were treated topically with an aldose reductase inhibitor had less pleomorphism and polymegethism. Using a different aldose reductase inhibitor, Meyer, Ubels, and Edelhauser[35] found that structural changes were prevented in rats with diabetes that were treated with aldose reductase inhibitor at the onset of diabetic induction; rats treated with aldose reductase inhibitor later in the course of diabetes showed partial reversal of diabetes-induced polymegethism and pleomorphism. These results suggested that the sorbitol pathway may be implicated in the cause of diabetic corneal endothelial alterations.

Yee and associates'[12] study of dogs with diabetes showed structural corneal endothelium changes similar to those of humans with diabetes, with the degree of change positively correlating with long-term glycemic control. This suggested that endothelial abnormalities may be related to hyperglycemia or insulin deficiency. In contrast, we did not detect a correlation between the degree of endothelial structural change and duration of disease or glycemic control. Matsuda and associates[33] also did not detect such a correlation. The apparent difference between dogs and humans may be related to the species variation or to tighter glycemic control and insufficient range of blood glucose levels in the human subjects.

Variations in endothelial structure alone do not necessarily translate into altered function or increased permeability. Young contact-lens wearers, for example, also have structural endothelial changes without a change in permeability.[36] Thus, variations in cell size and shape alone do not sufficiently explain increased endothelial permeability.

The concentration of fluorescein measured in the stroma at 8:00 A.M. was similar in the patients with diabetes and control subjects (Table). This finding indicated that the absorption of polar compounds topically administered into the cornea was not increased in these patients with diabetes. Absorption may be increased, however, in patients with more severe diabetes with retinal neovascularization and areas of nonperfusion.[8] The initial stromal fluorescein concentration is not a direct measure of corneal epithelial permeability because of many uncontrolled confounding variables. Conversely, our finding of similar initial stromal fluorescein concentrations in the two groups was consistent with the results of Stolwijk and associates,[9] who found no difference in corneal epithelial permeability between patients with diabetes and control subjects.

Hayashi and associates[37] reported a decrease in the aqueous humor flow rate in patients with diabetes. The mean flow rate was less in our subjects with diabetes than it was in the control subjects, but the difference did not reach statistical significance ($P = .08$). Hayashi and associates[37] noted that flow was decreased more when patients also had proliferative retinopathy; no subjects had proliferative disease in our study.

The intraocular pressure was significantly increased in the group with diabetes. Increased intraocular pressure in patients with diabetes has been reported by others,[38-40] although not all reports agree.[41-43] The tendency toward a lower aqueous humor flow rate in patients with diabetes, as discussed previously, would lower the intraocular pressure if outflow mechanisms were unaffected. Increased intraocular pressure accompanied by normal or decreased aqueous flow in diabetes implicates an effect of the disease on aqueous outflow pathways.

Autofluorescence of the cornea was increased in the patients with diabetes and was inversely correlated with the percentage of hexagonal cells. The increased corneal autofluorescence is consistent with the findings of Stolwijk and associates,[3] although the autofluorescence in their study was correlated with duration of diabetes. It is not known if the increased corneal autofluorescence in diabetes results from increased flavoprotein enzymes (the probable source of a major portion of corneal autofluorescence at the wavelengths measured[44,45] or from deposition of other fluorescent molecules in diabetic corneas.

The polarization of fluorescence by the cornea and by the anterior chamber was similar in the patients with diabetes and the control group. This finding indicated no difference between patients with diabetes and healthy subjects in the binding of fluorescein in corneas and anterior chambers. Regarding the anterior chambers, a similar concentration of albumin in the aqueous humors of patients with diabetes and control subjects was indicated.[21]

Given the protean manifestations of diabetes mellitus, clinical observations of abnormalities in diabetic corneas are not unexpected. Although the structure, and perhaps the metabolism, of the corneal endothelium are affected, sufficient reserve appears to exist to maintain normal function in the unstressed state.

References

1. Schwartz, D. E.: Corneal sensitivity in diabetics. Arch. Ophthalmol. 91:174, 1974.

2. Nobuo, I., Rao, G. N., del Cerro, M., and Aquavella, J. V.: Corneal nerve alterations in diabetes mellitus. Arch. Ophthalmol. 102:1380, 1984.

3. Stolwijk, T. R., Van Best, J. A., Boot, J. P., and Oosterhuis, J. A.: Corneal autofluorescence in diabetic and penetrating keratoplasty patients as measured by fluorophotometry. Exp. Eye Res. 51:403, 1990.

4. Hyndiuk, R. A., Kazarian, E. L., Schultz, R. O., and Seideman, S.: Neurotrophic corneal ulcers in diabetes mellitus. Arch. Ophthalmol. 95:2193, 1977.

5. Perry, H. D., Foulks, G. N., Thoft, R. A., and Tolentino, F. I.: Corneal complications after closed vitrectomy through the pars plana. Arch. Ophthalmol. 96:1401, 1978.

6. Michels, R. G., and Ryan, S. J.: Results and complications of 100 consecutive cases of pars plana vitrectomy. Am. J. Ophthalmol. 80:24, 1975.

7. Foulks, G. N., Thoft, R. A., Perry, H. D., and Tolentino, F. I.: Factors related to corneal epithelial complications after closed vitrectomy in diabetics. Arch. Ophthalmol. 97:1076, 1979.

8. Göbbels, M., Spitznas, M., and Oldendoerp, J.: Impairment of corneal epithelial barrier function in diabetics. Graefes Arch. Clin. Ophthalmol. 227:142, 1989.

9. Stolwijk, T. R., van Best, J. A., Boot, J. P., Lemkes, H. H. P. J., and Oosterhuis, J. A.: Corneal epithelial barrier function after oxybuprocaine provocation in diabetics. Invest. Ophthalmol. Vis. Sci. 31:436, 1990.

10. Olsen, T., Busted, N., and Schmitz, O.: Corneal thickness in diabetes mellitus. Lancet 1:883, 1980.

11. Schultz, R. O., Matsuda, M., Yee, R. W., Edelhauser, H. F., and Schultz, K. J.: Corneal endothelial changes in type I and type II diabetes mellitus. Am. J. Ophthalmol. 98:401, 1984.

12. Yee, R. W., Matsuda, M., Kern, T. S., Engerman, R. L., and Edelhauser, H. F.: Corneal endothelial changes in diabetic dogs. Curr. Eye Res. 4:759, 1985.

13. Rao, G. N., Aquavella, J. V., Goldberg, S. H., and Berk, S. L.: Pseudophakic bullous keratopathy. Relationships to preoperative endothelial status. Ophthalmology 91:1135, 1984.

14. Sweeny, D. F., Holden, B. A., Vannas, A., Efron, N., Swarbrick, H., Kotow, M., and Chan-Ling, T.: The clinical significance of corneal endothelial polymegethism. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1985, p. 53.

15. Carlson, K. H., and Bourne, W. M.: The clinical measurement of endothelial permeability. Cornea 7:183, 1988.

16. Lass, J. H., Spurney, R. V., Dutt, R. M., Andersson, H., Kochar, H., Rodman, H. M., Stern, R. C., and Doershuk, C. F.: A morphologic and fluorophotometric analysis of the corneal endothelium in type I diabetes mellitus and cystic fibrosis. Am. J. Ophthalmol. 100:783, 1985.

17. Watsky, M. A., McDermott, M. L., and Edelhauser, H. F.: In vitro corneal endothelial permeability in rabbit and human. The effects of age, cataract surgery, and diabetes. Exp. Eye Res. 49:751, 1989.

18. McLaren, J. W., and Brubaker, R. F.: A two-dimensional scanning ocular fluorophotometer. Invest. Ophthalmol. Vis. Sci. 26:144, 1985.

19. de Kruijf, E. J. F. M., Boot, J. P., Laterveer, L., van Best, J. A., Ramselaar, J. A. M., and Oosterhuis, J. A.: A simple method for determination of corneal epithelial permeability in humans. Curr. Eye Res. 6:1327, 1987.

20. Carlson, K. H., Bourne, W. M., McLaren, J. W., and Brubaker, R. F.: Variations in human corneal endothelial cell morphology and permeability to fluorescein with age. Exp. Eye Res. 47:27, 1988.

21. Herman, D. C., McLaren, J. W., and Brubaker, R. F.: A method of determining concentration of albumin in the living eye. Invest. Ophthalmol. Vis. Sci. 29:133, 1988.

22. Abraham, E. C., Perry, R. E., and Stallings, M.: Application of affinity chromatography for separation and quantitation of glycosylated hemoglobins. J. Lab. Clin. Med. 102:187, 1983.

23. Andersen, A. R., Christiansen, J. S., Andersen, J. K., Kreiner, S., and Deckert, T.: Diabetic nephropathy in type 1 (insulin dependent) diabetes. An epidemiological study. Diabetologia 25:496, 1983.

24. Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., and DeMets, D. L.: The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch. Ophthalmol. 102:520, 1984.

25. Krolewski, A. S., Warram, J. H., and Christlieb, A. R.: Onset, course, complications and prognosis of diabetes mellitus. In Marble, A., Krall, L. P., Bradley, R. F., Christlieb, A. R., and Soeldner, J. S. (eds.): Joslin's Diabetes Mellitus. Philadelphia, Lea & Febiger, 1985, pp. 251–277.

26. Lachin, J. M.: Introduction to sample size determination and power analysis for clinical trials. Controlled Clin. Trials 2:93, 1981.

27. Busted, N., Olsen, T., and Schmitz, O.: Clinical observations on the corneal thickness and the corneal endothelium in diabetes mellitus. Br. J. Ophthalmol. 65:687, 1981.

28. Vannas, A., Holden, B. A., Sweeney, D. F., Efron, N., and Polse, K. A.: Deswelling of the graft cornea following hypoxic oedema. Acta Ophthalmol. (Copenh.) 62:879, 1984.

29. Polse, K. A., Brand, R., Mandell, R., Vastine, D., Demartini, D., and Flom, R.: Age differences in corneal hydration control. Invest. Ophthalmol. Vis. Sci. 30:392, 1989.

30. Herse, P. R.: Corneal hydration control in normal and alloxan-induced diabetic rabbits. Invest. Ophthalmol. Vis. Sci. 31:2205, 1990.

31. Goebbels, M., and Spitznas, M.: Endothelial barrier function after phacoemulsification. A comparison between diabetic and non-diabetic patients. Graefes Arch. Clin. Exp. Ophthalmol. 229:254, 1991.

32. Itoi, M., Nakamura, T., Mizobe, K., Kodama, Y., Nakagawa, N., and Itoi, M.: Specular microscopic studies of the corneal endothelia of Japanese diabetics. Cornea 8:2, 1989.

33. Matsuda, M., Ohguro, N., Ishimoto, I., and Fukuda, M.: Relationship of corneal endothelial morphology to diabetic retinopathy, duration of diabetes and glycemic control. Jpn. J. Ophthalmol. 34:53, 1990.

34. Matsuda, M., Awata, T., Ohashi, Y., Inaba, M., Fukuda, M., and Manabe, R.: The effects of aldose reductase inhibitor on the corneal endothelial morphology in diabetic rats. Curr. Eye Res. 6:391, 1987.

35. Meyer, L. A., Ubels, J. L., and Edelhauser, H. F.: Corneal endothelial morphology in the rat. Effects of aging, diabetes, and topical aldose reductase inhibitor treatment. Invest. Ophthalmol. Vis. Sci. 29:940, 1988.

36. Carlson, K. H., Bourne, W. M., and Brubaker, R. F.: Effect of long-term contact lens wear on corneal endothelial cell morphology and function. Invest. Ophthalmol. Vis. Sci. 29:185, 1988.

37. Hayashi, M., Yablonski, M. E., Boxrud, C., Fong, N., Berger, C., and Jovanovic, L. J.: Decreased formation of aqueous humour in insulin-dependent diabetic patients. Br. J. Ophthalmol. 73:621, 1989.

38. Becker, B., Bresnick, G., Chevrette, L., Kolker, A. E., Oaks, M. C., and Cibis, A.: Intraocular pressure and its response to topical corticosteroids in diabetes. Arch. Ophthalmol. 76:477, 1966.

39. Klein, B. E. K., Klein, R., and Moss, S. E.: Intraocular pressure in diabetic persons. Ophthalmology 91:1356, 1984.

40. Krieger, N., Ketcher, G., and Fulk, G. W.: Physiological variables affecting intraocular pressure in a population study. Am. J. Optom. Physiol. Opt. 65:739, 1988.

41. Armaly, M. F., and Baloglou, P. J.: Diabetes mellitus and the eye. II. Intraocular pressure and aqueous outflow facility. Arch. Ophthalmol. 77:493, 1967.

42. Bankes, J. L. K.: Ocular tension and diabetes mellitus. Br. J. Ophthalmol. 51:557, 1967.

43. Bouzas, A. G., Gragoudas, E. S., Balodimos, M. C., Brinegar, C. H., and Aiello, L. M.: Intraocular pressure in diabetes. Relationship to retinopathy and blood glucose level. Arch. Ophthalmol. 85:423, 1971.

44. Laing, R. A., Fischbarg, J., and Chance, B.: Noninvasive measurements of pyridine nucleotide fluorescence from the cornea. Invest. Ophthalmol. Vis. Sci. 19:96, 1980.

45. Masters, B. R.: In vivo corneal redox fluorometry. In Masters, B. R. (ed.): Noninvasive Diagnostic Techniques in Ophthalmology. New York, Springer-Verlag, 1990, pp. 223–247.

Argon Laser Treatment of Trichiasis

George B. Bartley, M.D., and Jonathan C. Lowry, M.D.

The argon laser was used to treat trichiasis in 44 patients over a five-year period. During follow-up intervals of between one month and more than four years (mean, 13 months), ablation of misdirected cilia was accomplished with one treatment in 26 patients (59%). No complications were observed. Laser is less effective than cryotherapy for destroying aberrant eyelashes, but cryotherapy is less precise and incites greater posttreatment inflammation. Argon laser treatment is a useful option when only a few, scattered eyelashes require ablation or in patients with disorders such as ocular pemphigoid, in which the stimulation of inflammation is undesirable.

SYMPTOMATIC TRICHIASIS may be treated by several methods, including epilation, electrolysis, cryotherapy, surgery, or laser ablation.[1] Although cryotherapy is probably the most widely used and consistently effective therapeutic option in contemporary practice, it has the disadvantage of postoperative inflammation and the potential for eyelid notching, skin depigmentation, and other more serious sequelae.[2]

The treatment of trichiasis with the argon laser was first reported by Berry in 1979.[3] An advantage of laser ablation over cryotherapy is reduced inflammation because of precise tissue destruction, but early observations suggested that permanent extirpation of the misdirected cilia was less reliable.[1] Our study was undertaken to review the long-term results of treatment with the argon laser for trichiasis.

Patients and Methods

The medical records of 44 patients who underwent argon laser treatment for trichiasis by one of us (G.B.B.) during the five-year period from July 1986 through June 1991 were reviewed.

Misdirected eyelashes were ablated in the following manner. The eyelid in the region of trichiasis was anesthetized by an injection of 0.5 ml or less of 2% lidocaine with 1:100,000 epinephrine. The eyelid margin was everted away from the globe with a cotton-tipped applicator, and the patient was asked to gaze away from the planned area of treatment. An argon laser coupled to a slit-lamp biomicroscope was used to burn the trichiatic eyelash and follicle. The aiming beam was focused coaxial to the follicle of the cilium and burns were applied successively deeper into the eyelid substance. Laser variables were as follows: 1.0-W power, 50-μm spot size, 0.2-second duration, and blue-green wavelength.

The initial laser burn usually vaporized the eyelash and produced a small brown spot at the eyelid margin, which absorbed the energy from the subsequent burns. Approximately 20 to 30 additional burns, with a spot size of 100 μm in a few recent cases, were applied to each follicle. If the offending cilium was lightly pigmented, which sometimes prevented the laser energy from producing a burn, a drop of ink from a fountain pen was applied to the eyelash to facilitate uptake of the heat for the initial burn. Subsequent burns were then applied without difficulty. Antibiotic-corticosteroid ointment was applied to the eyelid margin at the conclusion of the procedure and two to three times daily during the next week.

Results

The average age of the 44 patients was 63 years (range, 30 to 86 years). Twenty-seven of

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the patients were women. Eight patients had previously been treated for trichiasis with cryotherapy, four patients had had misdirected eyelashes epilated, and the remaining 32 patients had not undergone previous treatment. The mean follow-up interval was 13 months (range, one month to more than four years).

In 27 patients, no apparent underlying cause for trichiasis was determined. In the remaining 17 patients, the aberrant cilia were associated with trauma (six patients), cicatricial ocular pemphigoid (three patients), herpes-zoster ophthalmicus (three patients), distichiasis (three patients), Stevens-Johnson syndrome (one patient), or alkali burn (one patient).

The results of treatment were considered satisfactory if the offending cilia were completely ablated or were considered unsatisfactory if regrowth of the treated eyelashes definitely or equivocally occurred. Twenty-six of the 44 patients (59%) had a satisfactory result with one treatment. Of the 18 patients (41%) who had an unsatisfactory result, five responded well to one additional argon-laser treatment to the recurrent cilia. Eight patients were treated with cryotherapy for persistent trichiasis; six of these eight patients had a satisfactory result with one treatment. In three of the 18 patients who had an unsatisfactory result after one argon laser treatment, the trichiasis persisted despite subsequent treatment with laser, cryotherapy, or both on two or more occasions. In two of the 18 patients, it was not possible to determine with certainty whether trichiasis identified on follow-up examination represented recurrence of treated eyelashes or the emergence of new misdirected cilia, so the treatment of these patients was considered to be a failure.

Treatment results were evaluated in terms of the underlying causes for trichiasis and generally reflected the overall success or failure distribution. Of particular interest were patients who had trichiasis associated with an inflammatory disorder; a satisfactory result was achieved after one treatment in one of the three patients with pemphigoid, two of the three patients with herpes-zoster ophthalmicus, and the one patient with Stevens-Johnson syndrome. Aside from recurrent trichiasis, no treatment-related complications were observed

Discussion

Although trichiasis in some patients is only a minor nuisance, in other patients it can be associated with marked corneal scarring and potential loss of visual acuity. Several treatment options may be considered, each with advantages and drawbacks.[1] Simple epilation of the misdirected eyelashes has no morbidity but does not usually effect a permanent cure because the cilia usually reappear within a week or two. Electrolysis is variably successful in destroying the treated follicle, but the procedure may be uncomfortable for the patient and is relatively tedious to perform.[4] Various surgical procedures have been described[5-12] to excise abnormal eyelashes, but an operation usually is reserved for patients with coexisting entropion or cases refractory to more conservative treatment. Radiotherapy has been reported to be highly effective in patients with severe trichiasis,[13,14] but currently is not favored by ophthalmologists.

Cryotherapy successfully ablates aberrant, misdirected cilia in 90% or more of affected patients and is a time-honored treatment.[2,15-26] Unfortunately, freezing may incite undesirable scarring that sometimes promotes eyelid margin entropion, particularly in patients with an underlying inflammatory disorder such as ocular pemphigoid or herpes-zoster ophthalmicus. The laser's ability to effect precise destruction of misdirected cilia, which was demonstrated clinically and histopathologically in an animal study,[1] theoretically should avoid some of the undesirable side effects of cryotherapy.

In 1979, Berry[3] described the use of the argon laser to treat trichiasis successfully in seven of eight patients. In 1980, Berry[27] reported that 21 cases had been treated with good results and indicated that more laser energy is necessary to ablate the misdirected eyelashes in lightly pigmented eyelids (0.8 to 1.0 W) than in patients with darker pigmentation (0.2 to 0.4 W). Neither report outlined the duration of application, the number of burns, or the duration of follow-up.

In 1986, Awan[28] studied 11 patients with trichiasis who were treated with the blue-green argon laser. A more recent study[29] provided updated information on a series of 31 patients. Lasers were used with 1.0- to 1.2-W power, 50- to 200-μm spot size, 0.1- to 0.2-second duration, and from 12 to 50 burns per follicle. During follow-ups ranging from three months to two years, the success rates achieved were 45% (14 of 31 patients) with one treatment and 90.3% (28 of 31 patients) with up to two additional applications. Treatment was considered successful "if no cilia reappeared in the laser-treated area after three months, or if a regrown eyelash did not cause any symptoms as a result of its extreme attenuation or change of direction away from the globe. . . ."[29] This is a clinically acceptable but more liberal standard than that used in our study.

In 1990, Campbell[30] reported the results of laser treatment of 15 eyelids in 12 patients. Five of the 15 eyelids (33%) were treated successfully with one application, and an 80% success rate (12 eyelids) was achieved with up to three treatments. No patients in the reports by Berry,[3,27] Awan,[28,29] or Campbell[30] had complications related to the laser.

Our study provided a large series of patients with a long follow-up period. Although the success rate with one treatment was only 59% (26 of the 44 patients), ablation of eyelashes was achieved with two treatments in 31 of the 44 patients (70%), and Awan[28] reported a success rate comparable to that of cryotherapy when up to three treatments were used. Because of the virtual absence of any complications related to the laser therapy, we believe that a recurrent eyelash can be treated several times with little fear of inducing marked scarring, in contrast to treatment with cryotherapy, in which undesirable side effects with multiple applications are likely. More recently, we have treated the eyelash follicle with a larger spot size (100 μm) and have directed the beam deeper into the eyelid margin. The initial results are promising, but an inadequate number of patients have been treated for meaningful comparative analysis.

The indications for cryotherapy or argon laser trichoablation are not identical. Cryotherapy is the preferred treatment option for most patients in our practice, especially when the trichiasis is idiopathic and the misdirected eyelashes are multiple and clustered in a small portion of the eyelid margin. In contrast, if only one or two cilia are aberrant, or if several eyelashes are widely distributed and treatment with cryotherapy would require more than one application along an otherwise normal eyelid margin, or if the patient has trichiasis associated with a cicatrizing condition such as ocular pemphigoid, then ablation with the argon laser is preferred. With respect to cost, our institution uses the same fee for both cryotherapy and argon laser trichoablation.

References

1. Bartley, G. B., Bullock, J. D., Olsen, T. G., and Lutz, P. D.: An experimental study to compare methods of eyelash ablation. Ophthalmology 94:1286, 1987.

2. Wood, J. R., and Anderson, R. L.: Complications of cryosurgery. Arch. Ophthalmol. 99:460, 1981.

3. Berry, J.: Recurrent trichiasis. Treatment with laser photocoagulation. Ophthalmic Surg. 10:36, 1979.

4. Scheie, H. G., and Albert, D. M.: Distichiasis and trichiasis. Origin and management. Am. J. Ophthalmol. 61:718, 1966.

5. Fein, W.: Surgical repair for distichiasis, trichiasis, and entropion. Arch. Ophthalmol. 94:809, 1976.

6. Hill, J. C.: Trichiasis and distichiasis. Can. J. Ophthalmol. 11:53, 1976.

7. Clorfeine, G. S., and Kielar, R. A.: Lash excision in trichiasis. Ann. Ophthalmol. 9:525, 1977.

8. Dortzbach, R. K., and Butera, R. T.: Excision of distichiasis eyelashes through a tarsoconjunctival trapdoor. Arch. Ophthalmol. 96:111, 1978.

9. Anderson, R. L., and Harvey, J. T.: Lid splitting and posterior lamella cryosurgery for congenital and acquired distichiasis. Arch. Ophthalmol. 99:631, 1981.

10. Silver, B.: The use of mucous membrane from the hard palate in the treatment of trichiasis and cicatricial entropion. Ophthalmic Plast. Reconstr. Surg. 2:129, 1986.

11. Wolfley, D.: Excision of individual follicles for the management of congenital distichiasis and localized trichiasis. J. Pediatr. Ophthalmol. Strabismus 24:22, 1987.

12. Bartley, G. B., and Jackson, I. T.: Distichiasis and cleft palate. Plast. Reconstr. Surg. 84:129, 1989.

13. Lamb, A.: Keratoplasty and trichiasis. The permanent destruction of eyelashes by radiotherapy. Trans. Ophthalmol. Soc. Aust. 24:100, 1965.

14. Hartzler, J., Neldner, K. H., and Forstot, S. L.: X-ray epilation for the treatment of trichiasis. Arch. Dermatol. 120:620, 1984.

15. Sullivan, J. H., Beard, C., and Bullock, J. D.: Cryosurgery for treatment of trichiasis. Am. J. Ophthalmol. 82:117, 1976.

16. ———: Cryosurgery for treatment of trichiasis. Trans. Am. Ophthalmol. Soc. 74:189, 1976.

17. Fraunfelder, F. T., Wallace, T. R., Farris, H. E., Watkins, J. III, Hendrickson, R., Smead, W. J., and Limmer, B. L.: The role of cryosurgery in external ocular and periocular disease. Trans. Am. Acad. Ophthalmol. Otolaryngol. 83:OP713, 1977.

18. Sullivan, J. H.: The use of cryotherapy for trichiasis. Trans. Am. Acad. Ophthalmol. Otolaryngol. 83:OP708, 1977.

19. Hecht, S. D.: Cryotherapy of trichiasis with use of the retinal cryoprobe. Ann. Ophthalmol. 9:1501, 1977.

20. Fraunfelder, F. T., and Petursson, G. J.: The use of liquid nitrogen cryospray for treatment of trichiasis. Ophthalmic Surg. 10:42, 1979.

21. Frueh, B. R.: Treatment of distichiasis with cryotherapy. Ophthalmic Surg. 12:100, 1981.

22. Majekodunmi, S.: Cryosurgery in treatment of trichiasis. Br. J. Ophthalmol. 66:337, 1982.

23. Delaney, M. R., and Rogers, P. A.: A simplified

cryotherapy technique for trichiasis and distichiasis. Aust. J. Ophthalmol. 12:163, 1984.

24. Johnson, R. L. C., and Collin, J. R. O.: Treatment of trichiasis with a lid cryoprobe. Br. J. Ophthalmol. 69:267, 1985.

25. Peart, D. A., and Hill, J. C.: Cryosurgery for trichiasis in black patients. Br. J. Ophthalmol. 70:712, 1986.

26. Rice, C. D., Kersten, R. C., and Al-Hazzaa, S.: Cryotherapy for trichiasis in trachoma. Arch. Ophthalmol. 107:1180, 1989.

27. Berry, J.: Argon laser office procedures. South. Med. J. 73:1672, 1980.

28. Awan, K. J.: Argon laser treatment of trichiasis. Ophthalmic Surg. 17:658, 1986.

29. ———: Laser photocoagulation-vaporization therapy of trichiasis. Ophthalmic Laser Ther. 3:3, 1988.

30. Campbell, D. C.: Thermoablation treatment for trichiasis using the argon laser. Aust. N.Z. J. Ophthalmol. 18:427, 1990.

Ophthalmic miniature

OKW-, to see, whence Gc EYE and DAISY, the ''day's eye'' . . .; also WINDOW, the ''wind's eye'' (you see out of it—and the wind blows into it). From L we get EYELET (''little eye''), INVEIGLE (''blind the eyes of'' . . .), and INOCULATE—originally, implant an ''eye'' (bud or graft); now, ''implant'' a microbe or vaccine. From various Gk words for eye we get a host of medico-scientific terms, of which the best known are -OPIA (as in ''myopia'') and OPHTHALMO- (as in ''ophthalmologist''). More generally known are terms from Gk *opsis*, *opt-*, sight, seeing, whence OPTIC, SYNOPSIS (''seeing [everything] together''), and AUTOPSY, literally ''seen by an eyewitness''; the present sense is idiomatic.

Robert Claiborne, *The Roots of English:*
A Reader's Handbook of Word Origins
New York, Doubleday, 1989, pp. 179–180

Immune Deposits in Iris Biopsy Specimens From Patients With Fuchs' Heterochromic Iridocyclitis

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To investigate whether Fuchs' heterochromic iridocyclitis may be an immune complex vasculitis, we used an immunofluorescence technique to detect immunoglobulins and complement in iris biopsy specimens from nine patients with Fuchs' heterochromic iridocyclitis, 12 patients with other types of uveitis, and nine patients with glaucoma but without uveitis. No specific immune deposits were observed in the irises of the patients with Fuchs' heterochromic iridocyclitis. Immunoglobulin G, IgA, IgM, and complement were detected in patients with Fuchs' heterochromic iridocyclitis and patients with uveitis, and these results differed significantly ($P < .05$) from the group without uveitis. The immune deposits were found only in the iris vessel walls. No light-microscopic evidence of an inflammatory vascular process could be detected. Further studies are necessary to investigate whether the immune reactants originate from the circulation or result from local formation.

FUCHS' HETEROCHROMIC IRIDOCYCLITIS is still a distinct clinical entity of unknown origin. It is characterized by a mostly unilateral, chronic, low-grade anterior uveitis and a variable degree of atrophy and depigmentation of the iris stroma and pigment epithelium. Other typical findings include the widely scattered small keratic precipitates and the absence of synechiae. Subcapsular cataract is often present and Fuchs' heterochromic iridocyclitis is complicated by glaucoma in 15% to 20% of cases.[1-4]

A vascular pathogenesis involving the iris vessels is one of the hypotheses for the cause of Fuchs' heterochromic iridocyclitis.[5] The characteristic filiform hemorrhage seen after anterior chamber paracentesis (Amsler's sign) was the first vascular abnormality described in patients with this disease.[6] Later, iris fluorescein angiographic studies showed distinct, mainly peripupillary fluorescein leakage, delayed filling, and sectors of ischemia frequently associated with neovascularization.[7,8]

Light microscopy disclosed abnormal hyalinization and sometimes endothelial proliferation of the iris vessel walls, with narrowing of the vessel lumen.[1,5,9,10] This narrowing of the vessel lumen, ultimately leading to occlusion, may be the result of immune complex deposition, and Fuchs' heterochromic iridocyclitis may be an immune complex vasculitis.[5,11]

Immune complexes have been detected in the aqueous humor and serum of patients with Fuchs' heterochromic iridocyclitis.[12,13] Plasma cells[9,14-19] present in the iris may be responsible for the local production of antibodies, subsequently leading to intraocular immune complex formation.[5,10]

Little evidence has been provided concerning an immune complex vasculitis of the iris vessels in patients with Fuchs' heterochromic iridocyclitis. We investigated this hypothesis by using an immunofluorescence technique to demonstrate deposits of immunoglobulins and complement in iris biopsy specimens from patients with Fuchs' heterochromic iridocyclitis. Results were compared with those of patients without uveitis and of patients with other types of uveitis.

Material and Methods

Iris biopsy specimens (from peripheral iridectomies) were obtained from nine patients with

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CENTRAL

Fuchs' heterochromic iridocyclitis (mean age ± standard deviation, 39.1 ± 15.9; range, 25 to 77 years; four women and five men), and 12 patients with other types of uveitis (mean age ± standard deviation, 56.1 ± 21.6; range, 22 to 88 years; eight women and four men), classified according to the recommendations of the International Uveitis Study Group.[20] Diagnoses included chronic anterior uveitis (four patients, in one of whom the uveitis was associated with juvenile chronic arthritis), recurrent anterior uveitis (three patients, in two of whom the uveitis was associated with HLA-B27), idiopathic panuveitis (four patients), and one patient with phacogenic uveitis. At the time of the operation, no patients with Fuchs' heterochromic iridocyclitis were being treated systemically, but two were using corticosteroid eyedrop preparations, and one was using antiglaucoma eyedrops. Of the 12 patients with other types of uveitis, two were being treated with systemic noncorticosteroid anti-inflammatory drugs, seven were being treated with corticosteroid eyedrop preparations, and three patients were being treated with antiglaucoma eyedrops at the time of the operation.

Iris specimens were also obtained from nine patients without uveitis (mean age ± standard deviation, 58.6 ± 17.5; range, 31 to 83 years; five women and four men) who had primary open-angle glaucoma and were undergoing trabeculectomy. None of these patients was treated systemically and all patients were using antiglaucoma eyedrops at the time of the operation. We chose patients with glaucoma as controls, rather than patients undergoing extracapsular cataract extraction for nuclear age-related cataract, because peripheral iridectomy is an integral part of trabeculectomy. All patients were informed of these investigations and their consent was obtained.

All specimens were snap-frozen in optimal cutting-tissue compound within one hour of iridectomy. Four-micrometer-thick cryostat sections were fixed in acetone for ten minutes and subsequently air-dried and rinsed in phosphate-buffered saline solution (pH, 7.4). Slides were then incubated for one hour at room temperature (20 C) with a panel of polyclonal rabbit antibodies in phosphate-buffered saline solution containing 0.02% gelatin and 0.1% sodium azide. The following antibodies were used: antihuman IgG, IgA, and IgM, all labeled with fluorescein isothiocyanate (De Beer Medicals, Hilvarenbeek, The Netherlands), used in a direct (one-step) method, and antihuman complement (C3c + C3d + C4), fibrinogen, C1q, and C3 (Central Laboratory of the Red Cross Blood-transfusion Service, Amsterdam, The Netherlands) used in an indirect (two-step) method. Normal rabbit serum (Dakopatts, Glostrup, Denmark) was used as a negative control. For the second step, after rinsing the slides in phosphate-buffered saline solution, they were incubated for one-half hour at room temperature (20 C) with fluorescein isothiocyanate–labeled polyclonal horse antirabbit immunoglobulins. Subsequently, all slides were rinsed in phosphate-buffered saline solution.

One slide from each specimen was stained with hematoxylin and eosin to evaluate the following pathologic features typical of Fuchs' heterochromic iridocyclitis: (1) the presence of inflammatory cells; (2) iris stromal atrophy and fibrosis; (3) disappearance of stromal melanocytes; (4) focal depigmentation of the iris pigment epithelium; and (5) hyalinization of the vessel walls, as described in an earlier study.[21] This stain was also used for the evaluation of the light-microscopic signs characteristic of vasculitis. These clinical signs are defined as neutrophilic or lymphocytic and plasmacellular invasion of the vessel wall with fibrinoid necrosis or fibrous thickening.[22,23]

Tissue sections were examined with a fluorescence microscope using a ×25 magnification in a masked fashion by two of us (E.L.H. and C.M.M.) who were unaware of the diagnosis. Immunofluorescence staining in a granular pattern in the vessel wall was considered positive, whereas it was considered negative in the absence of fluorescence or if a homogeneous staining pattern resulting from diffusion of plasma from the lumen was present. Comparison between the three groups was performed by using the Fisher's exact test.

Results

The granular deposition of immunoglobulins, complement, and fibrinogen in the vascular walls of the iris vessels in the iris biopsy specimens of all groups was determined (Table). No extracellular immune deposits were observed outside the vessel walls. The findings in patients with Fuchs' heterochromic iridocyclitis did not differ significantly from those in patients with other types of uveitis.

Immunoglobulin G, IgA, C3, fibrinogen ($P < .05$), IgM ($P < .01$), and complement ($P = .001$)

TABLE

IMMUNE DEPOSITS IN IRIS VESSEL WALLS OF PATIENTS WITH FUCHS' HETEROCHROMIC IRIDOCYCLITIS, PATIENTS WITH UVEITIS, AND PATIENTS WITH GLAUCOMA

IMMUNE DEPOSITS	NO. OF DEPOSITS IN PATIENTS WITH FUCHS' HETEROCHROMIC IRIDOCYCLITIS (N=9)	DIFFERENCE*	NO. OF DEPOSITS IN PATIENTS WITH UVEITIS (N=12)	DIFFERENCE†	NO. OF DEPOSITS IN PATIENTS WITH GLAUCOMA (N=9)
IgG	4	P = .041	1	P = .571	0
IgA	4	P = .041	4	P = .083	0
IgM	7	P = .007	6	P = .072	1
Complement	7	P = .001	5	P = .039	0
C1q	2	P = .235	3	P = .165	0
C3	4	P = .041	4	P = .083	0
Fibrinogen	4	P = .041	6	P = .017	0

*Difference between patients with Fuchs' heterochromic iridocyclitis and patients with glaucoma.

†Difference between patients with uveitis and patients with glaucoma.

were found in a significantly higher number of irises obtained from patients with Fuchs' heterochromic iridocyclitis than in irises obtained from patients with glaucoma but without uveitis (Fig. 1). Complement and fibrinogen were the only immune deposits found in a significantly higher ($P < .05$) number of irises from patients with uveitis than in irises obtained from patients with glaucoma but without uveitis (Fig. 2). Plasma cells containing IgG, IgA, or IgM were found in the iris stroma of four of nine irises obtained from patients with Fuchs' heterochromic iridocyclitis and in six of the 12 irises from patients with uveitis. Immunoglobulin G, IgA, and IgM were equally distributed in the plasma cells of both groups. No immunoglobulin-containing plasma cells could be detected in the irises obtained from patients with glaucoma but without uveitis.

No correlation could be seen between those patients treated with corticosteroids and the presence or absence of specific immune deposits. However, in the two patients with uveitis who were treated with systemic noncorticosteroid anti-inflammatory drugs, no immune deposits were found.

Pathologic features typical of Fuchs' heterochromic iridocyclitis (Fig. 3) were observed with hematoxylin and eosin staining in eight of the nine irises obtained from patients with Fuchs' heterochromic iridocyclitis. No characteristics of vasculitis were observed by light microscopy in any of the iris biopsy specimens. Scattered deposits of infiltrating mononuclear cells (chiefly lymphocytes and plasma cells) were observed in the iris stroma and anterior iris border layer, but not in the vessel walls, of all irises obtained from patients with Fuchs' heterochromic iridocyclitis or uveitis. In six of the nine irises from control patients (patients with glaucoma but without uveitis), a few isolated mononuclear cells were observed in the iris stroma. Hyalinization of the iris vessel walls was observed in the irises of all patients with Fuchs' heterochromic cyclitis or uveitis. The vessel walls of four irises from patients with glaucoma also had some degree of hyalinization. No endothelial proliferation of the iris vessel walls was found in any of the iris biopsy specimens.

Discussion

Deposits of immunoglobulins and complement were observed in the vessel walls of the irises of patients with Fuchs' heterochromic iridocyclitis. However, no specific immunofluorescence staining pattern could be identified in the irises of patients with Fuchs' heterochromic iridocyclitis. The immune deposits observed in patients with Fuchs' heterochromic iridocyclitis were similar to those found in the patients with uveitis.

Although the only acceptable proof for the demonstration of immune complexes is the detection of the antigen involved, the deposition of both immunoglobulins and complement suggests the presence of immune complexes in the vessel walls of the iris. These immune complexes may either be formed within the eye or result

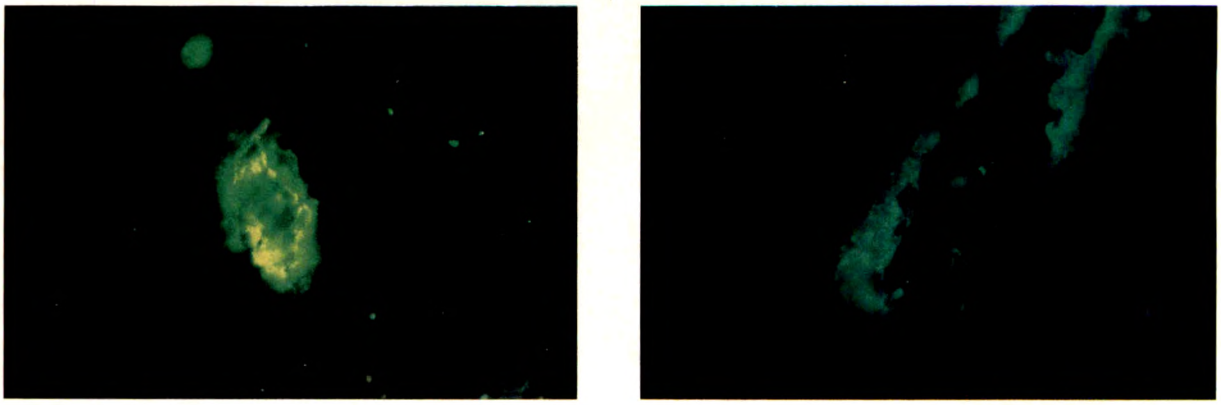

Fig. 1 (La Hey and associates). Iridectomy specimen from a patient with Fuchs' heterochromic iridocyclitis. Left, Granular IgM deposits in vessel wall (× 630). Right, Granular IgA deposits in vessel wall (× 630).

from the deposition of circulating immune complexes in the iris vessel walls.

Earlier studies demonstrated circulating immune complexes in the serum and aqueous humor of patients with Fuchs' heterochromic iridocyclitis.[11,12] Circulating immune complexes are associated with many autoimmune diseases. Recently detected cellular and humoral immunity directed against corneal antigens suggest a role of autoimmune reactions in the pathogenesis of Fuchs' heterochromic iridocyclitis.[24,25] However, patients with Fuchs' heterochromic iridocyclitis are generally free of the more commonly encountered systemic manifestations of immune complex disease such as arthritis, glomerulonephritis, or scleritis.[5] Moreover, in patients with systemic vasculitic syndromes such as systemic lupus erythematosus, ocular manifestations are uncommon.[26] It is difficult to implicate circulating immune complexes in a disease that is usually unilateral, unless there are conditions of the vessel walls of the already affected iris that promote binding of immune complexes.[5]

The typical perivascular distribution of the immune deposits and the absence of these deposits in the surrounding iris tissue suggest that the immune reactants originate from the circulation and are not formed within the iris stroma. Because the presence of the immune deposits was limited to the vessel walls, it seems likely that, if circulating immune complexes are involved in the pathogenesis of Fuchs' heterochromic iridocyclitis, these com-

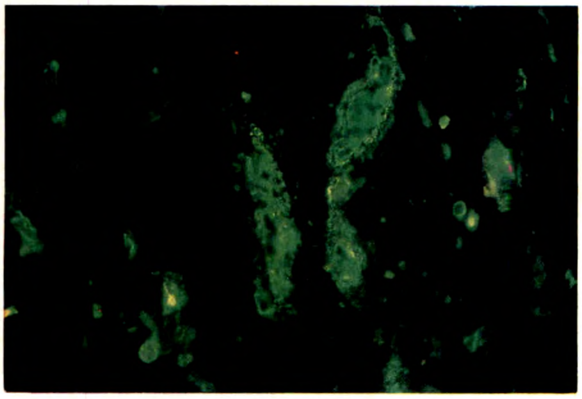

Fig. 2 (La Hey and associates). Iridectomy specimen from a patient with idiopathic recurrent anterior uveitis. Granular fibrinogen deposits in vessel walls (× 400).

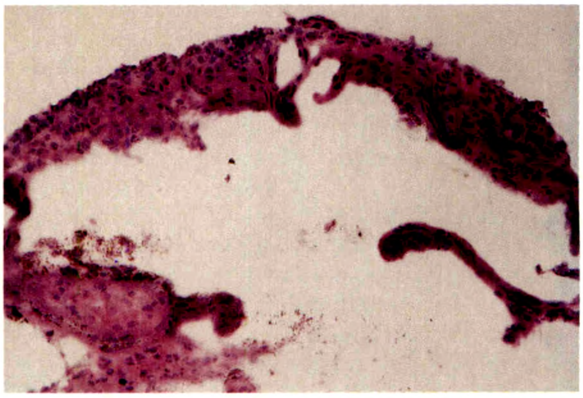

Fig. 3 (La Hey and associates). Iridectomy specimen from a patient with Fuchs' heterochromic iridocyclitis with the following typical pathologic features: stromal atrophy, stromal fibrosis, no stromal melanocytes, depigmentation of the posterior pigment epithelium, and infiltrating mononuclear cells (chiefly lymphocytes and plasma cells) in the stroma and anterior border layer (hematoxylin and eosin, × 250).

plexes bind to a structure expressed on the membrane of the iris vascular endothelial cells, such as the receptor for the first complement subcomponent (C1q) described by Daha and associates[27] on cultured human umbilical vein endothelial cells.

Recent investigations of systemic vasculitis focused on the presence of antiendothelial cell autoantibodies. Sera from patients with systemic lupus erythematosus contained complement-fixing antibodies and immune complexes that could bind themselves to cultured human umbilical vein endothelial cells.[28] Antiendothelial cell antibodies have also been found in 70% of patients with rheumatoid arthritis and vasculitis and in children with active Kawasaki syndrome, a diffuse vasculitis.[29-31] These antiendothelial cell antibodies lyse cultured vascular endothelial cells only when these cells have been exposed previously to gamma interferon, interleukin-1, or tumor necrosis factor. These inflammatory mediators probably induce certain target antigens on the endothelial cells.[31] The presence of two cytokines, interleukin-2, and gamma interferon, was recently demonstrated in the eyes of patients with uveitis.[32,33] High concentrations of the cytokine Il-6 have been found in the aqueous humor of patients with Fuchs' heterochromic iridocyclitis.[34] Therefore, it would be interesting to investigate whether antiendothelial cell antibodies are present in the serum and aqueous humor of patients with Fuchs' heterochromic iridocyclitis.

Recent studies indicated that human vascular endothelial cells synthesize and secrete complement factors. Both activators (C3) and inhibitors (factor H) are produced and their production is regulated by cytokines (interleukin-1, gamma-interferon).[35,36] Therefore, the deposits of C3 we observed in the walls of the iris vessels may have either originated from the circulation, or resulted from local (de novo) synthesis by the activated endothelial cells of the iris vessels.

Although earlier iris fluorescein angiographic studies of Fuchs' heterochromic iridocyclitis clearly demonstrated leakage from the iris vessels,[7,8] we found no light-microscopic evidence of a vasculitic process. The hyalinization of iris vessel walls we found in all our patients with Fuchs' heterochromic iridocyclitis or uveitis was also seen to some degree in the irises of patients with glaucoma and may not have been an abnormal finding.[21] Immunoglobulin deposition in vessel walls is known to be associated with several autoimmune disorders, but it is not clear with light microscopy what these deposits mean in the absence of an inflammatory vascular process. In a recent study on temporal arteritis, it was suggested that positive direct immunofluorescence microscopy on temporal artery biopsies with negative light microscopy identifies subclinical temporal arteritis.[37] In Henoch-Schönlein purpura, a systemic IgA-mediated immune complex vasculitis, IgA was found in the vessel walls of 78% of the normal-appearing skin biopsy specimens.[38]

No specific immune deposits could be identified in the irises of patients with Fuchs' heterochromic iridocyclitis as compared with the findings in irises of other patients with uveitis. A recent analysis of iris biopsy specimens also failed to show any specific immunohistologic abnormalities in Fuchs' heterochromic iridocyclitis as compared with the findings in other uveitis entities.[21] Therefore, although Fuchs' heterochromic iridocyclitis may be a single clinical entity, it may not be caused by one specific (immuno) pathogenic mechanism.

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References

1. Fuchs, E.: Ueber komplikationen der heterochromie. Z. Augenheilkd. 15:14, 1906.

2. Dernouchamps, J. P.: Fuchs' heterochromic cyclitis. An IUSG study about 550 cases. In Saari, K. M. (ed.): Uveitis Update. Amsterdam, Elsevier Science Publishers B.V., 1984, pp. 129–135.

3. Loewenfeld, I. E., and Thompson, H. S.: Fuchs's heterochromic cyclitis. A critical review of the literature. I. Clinical characteristics of the syndrome. Surv. Ophthalmol. 17:394, 1973.

4. ——: Fuchs' heterochromic cyclitis. A critical review of the literature. II. Etiology and mechanisms. Surv. Ophthalmol. 18:2, 1973.

5. O'Connor, G. R.: Doyne lecture. Heterochromic iridocyclitis. Trans. Ophthalmol. Soc. U.K. 104:219, 1985.

6. Amsler, M., and Verrey, F.: Heterochromie de Fuchs' et fragilite vasculaire. Ophthalmologica 111:177, 1946.

7. Saari, M., Vourre, I., and Nieminen, H.: Fuchs' heterochromic cyclitis. A simultaneous bilateral angiographic study of the iris. Br. J. Ophthalmol. 62:715, 1978.

8. Berger, B. B., Tessler, H. H., and Kottow, M. H.: Anterior segment ischemia in Fuchs' heterochromic cyclitis. Arch. Ophthalmol. 98:499, 1980.

9. Goldberg, M. F., and Erozan, Y. S.: Cytopathologic and histopathologic aspects of Fuchs' heterochromic cyclitis. Arch. Ophthalmol. 74:604, 1965.

10. Franceschetti, A.: Heterochromic cyclitis. Am. J. Ophthalmol. 39:50, 1955.

11. Murray, P. I.: Immunology of Fuchs' heterochromic cyclitis. In Ferraz de Oliveira, L. N. (ed.): Ophthalmology Today. Amsterdam, Elsevier Science Publishers B.V., 1988, pp. 63–66.

12. Dernouchamps, J. P., Vaerman, J. P., Michiels, J., and Masson, P. L.: Immune complexes in the aqueous humor and serum. Am J. Ophthalmol. 84:24, 1977.

13. Murray, P. I., Dinning, W. J., and Rahi, A. H. S.: Immune responses in heterochromic cyclitis. In Secchi, A. G., and Fregona, J. A. (eds.): Modern Trends in Immunology and Immunopathology of the Eye. Milan, Masson, 1989, pp. 295–297.

14. Kimura, S. J., Hogan, M. J., and Thygeson, P.: Fuchs' syndrome of heterochromic cyclitis. Arch. Ophthalmol. 54:179, 1955.

15. Makley, T. A.: Heterochromic cyclitis in identical twins. Am. J. Ophthalmol. 41:768, 1956.

16. Doughman, D. J.: Fuchs' heterochromia. Surv. Ophthalmol. 11:297, 1966.

17. Wobman, P.: Die heterochromiecyclitis Fuchs. Elektronen-mikroskopische studie von 9 irisbiopsien. Graefes Arch. Clin. Exp. Ophthalmol. 199:167, 1976.

18. Melhamed, S., Lahev, M., Sandbank, U., Yassur, Y., and Ben-Sira, I.: Fuchs' heterochromic iridocyclitis. An electron microscopic study of the iris. Invest. Ophthalmol. Vis. Sci. 17:1193, 1978.

19. McCartney, A. C. E., Bull, T. B., and Spalton, D. J.: Fuchs' heterochromic cyclitis. An electron microscopic study. Trans. Ophthalmol. Soc. U.K. 105:324, 1986.

20. Bloch-Michel, E., and Nussenblatt, R. B.: International uveitis study group recommendations for the evaluation of intraocular inflammatory disease. Am. J. Ophthalmol. 103:234, 1987.

21. Murray, P. I., Mooy, C. M., Visser-de Jong, E., Baarsma, G. S., de Vries, J., de Jong, P. T. V. M., and Kijlstra, A.: Immunohistochemical analysis of iris biopsy specimens from patients with Fuchs' heterochromic cyclitis. Am. J. Ophthalmol. 109:394, 1990.

22. Fauci, A. S.: The spectrum of vasculitis. Clinical, pathologic, immunologic and therapeutic considerations. Ann. Intern. Med. 89:660, 1978.

23. Tsokos M, Lazarou, S. A., and Moutsopoulos, H. M.: Vasculitis in primary Sjogren's syndrome. Am. J. Clin. Pathol. 88:26, 1987.

24. van der Gaag, R., Broersma, L., Rothova, A., and Kijlstra, A.: Immunity to a corneal antigen in Fuchs' heterochromic cyclitis patients. Invest. Ophthalmol. Vis. Sci. 30:443, 1989.

25. La Hey, E., Baarsma, G. S., Rothova, A., Broersma, L., van der Gaag, R., and Kijlstra, A.: High incidence of corneal epithelium antibodies in Fuchs' heterochromic cyclitis. Br. J. Ophthalmol. 72:921, 1988.

26. Gold, D. H., Morris, D. A., and Henkind, P.: Ocular findings in systemic lupus erythematosus. Br. J. Ophthalmol. 56:800, 1972.

27. Daha, M. R., Miltenburg, A. M. M., Hiemstra, P. S., Klar-Mohamed, N., van Es, L. A., and van Hinsbergh, V. W. M.: The complement subcomponent C1q mediates binding of immune complexes and aggregates to endothelial cells in vitro. Eur. J. Immunol. 18:783, 1988.

28. Cines, D. B., Lyss, A. P., Reeber, M., Bina, M., and Dehoratius, R. J.: Presence of complement-fixing anti-endothelial cell antibodies in systemic lupus erythematosus. J. Clin. Invest. 73:611, 1984.

29. Heurkens, A. H. M., Hiemstra, P. S., Lafeber, G. J. M., Daha, M. R., and Breedveld, F. C.: Anti-endothelial cell antibodies in patients with rheumatoid arthritis complicated by vasculitis. Clin. Exp. Immunol. 78:7, 1989.

30. Leung, D. Y. M., Collins, T., Lapierre, L. A., Geha, R. S., and Pober, J. S.: Immunoglobulin M antibodies present in the acute phase of Kawasaki syndrome lyse cultured vascular endothelial cells stimulated by g-interferon. J. Clin. Invest. 77:1428, 1986.

31. Leung, D. Y. M., Geha, R. S., Newburger, J. W., Burns, J. C., Fiers, W., Lapierre, L. A., and Pober, J. S.: Two monokines, interleukin 1 and tumor necrosis factor, render cultured vascular endothelial cells susceptible to lysis by antibodies circulating during Kawasaki syndrome. J. Exp. Med. 164:1958, 1986.

32. Hooks, J. J., Chan, C. C., and Detrick, B.: Identification of the lymphokines, interferon-gamma and interleukin-2, in inflammatory eye diseases. Invest. Ophthalmol. Vis. Sci. 29:1444, 1988.

33. Abi-Hanna, D., McCluskey, P., and Wakefield, D.: HLA-antigen in the iris and aqueous humor gamma-interferon levels in anterior uveitis. Invest. Ophthalmol. Vis. Sci. 30:990, 1989.

34. Murray, P. I., Hoekzema, R., van Haren, M. A. C., de Hon, F. D., and Kijlstra, A.: Aqueous humor interleukin-6 levels in uveitis. Invest. Ophthalmol. Vis. Sci. 31:917, 1990.

35. Brooimans, R. A., van der Ark, A. A. J., Buurman, W. A., van Es, L. A., and Daha, M. R.: Differential regulation of complement factor H and C3 production in human umbilical vein endothelial cells by IFN-γ and IL-1. J. Immunol. 144:3835, 1990.

36. Brooimans, R. A., Hiemstra, P. S., van der Ark, A. A. J., Sim, R. B., van Es, L. A., and Daha, M. R.: Biosynthesis of complement factor H by human umbilical vein endothelial cells. J. Immunol. 142:2024, 1989.

37. Wells, K. K., Folberg, R., Goeken, J. A., and Kemp, J. D.: Temporal artery biopsies. Correlation of light microscopy and immunofluorescence microscopy. Ophthalmology 96:1058, 1989.

38. Van Hale, H. M., Gibson, L. E., and Schroeter, A. L.: Henoch Schonlein vasculitis. Direct immunofluorescence study of uninvolved skin. J. Am. Acad. Dermatol. 15:665, 1986.

Semiconductor Diode Laser Transscleral Cyclophotocoagulation in Patients With Glaucoma

Hugh L. Hennis, M.D., and William C. Stewart, M.D.

We used the semiconductor diode laser to perform transscleral cyclophotocoagulation in 14 patients with glaucoma. Laser settings used for this procedure were 990 milliseconds, 100-μm spot size, and 1,200 mW of power. Applications were placed 1 mm posterior to the surgical corneoscleral limbus and 1 mm defocused toward the ciliary body. The mean preoperative intraocular pressure was 34.8 ± 13 mm Hg, and the mean intraocular pressure six months after a single treatment session was 24.3 ± 18 mm Hg ($P > .001$, paired *t*-test). The mean number of glaucoma medications decreased from 2.2 preoperatively to 1.4 postoperatively. Complications included conjunctival burns and uveitis in 14 patients, and pain in one patient. These results suggested that semiconductor diode transscleral cyclophotocoagulation may be useful as a treatment to reduce the intraocular pressure in patients with glaucoma.

TRANSSCLERAL CYCLOPHOTOCOAGULATION using laser energy may be effective in reducing the intraocular pressure in patients with glaucoma in whom filtering operations have a poor prognosis or are not indicated. This procedure has been performed successfully in the past using ruby, argon-krypton, and Nd:YAG laser energy.

We evaluated the transscleral cyclodestructive effects of a semiconductor diode laser to determine its safety and efficacy in decreasing the intraocular pressure in patients with glaucoma.

Material and Methods

Patients with glaucoma who underwent semiconductor diode transscleral cyclophotocoagulation and who were treated by us were included in this study. This procedure was recommended to preserve vision or relieve pain in patients who needed a reduction in intraocular pressure despite maximal tolerated medical therapy and argon laser trabeculoplasty. Filtering operations were not recommended to preserve vision because of poor prognosis. Initially, treatments were performed in patients who had no light perception or light perception visual acuity only. Later, however, patients with better visual acuity also were included in this study. Each patient signed an informed consent for this procedure after an explanation of the potential risks and benefits.

We used the Microlase laser, which incorporates two infrared laser diodes with a wavelength of 780 to 830 nm and is used as a slit-lamp attachment. It has a power capability of 0 to 1,200 mW, a pulse duration of 0 to 990 milliseconds, and a spot size of 100 to 500 μm.

Before each operation, each patient had an ocular and medical history taken and underwent an examination that included the inspection of the ocular adnexa, Goldmann applanation tonometry, slit-lamp biomicroscopy, Snellen visual acuity, and ophthalmoscopy.

Semiconductor diode transscleral cyclophotocoagulation was performed in the after manner. The patient was given a retrobulbar anesthetic consisting of 3.5 ml of bupivacaine 0.75%. A Barraquer speculum was used to separate the eyelids. The patient then was placed at the biomicroscope, and laser applications were applied parallel to the visual axis without the use of a contact lens. The laser system was focused on the sclera 1 mm from the surgical corneoscleral limbus with Castroviejo calipers and then defocused posteriorly 1 mm, as measured by a millimeter rule at the base of the biomicroscope.

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The laser variables used in this study were similar to those evaluated previously to create thermal lesions in the ciliary processes of cadaver eyes and included a 100-μm spot size, a 990-millisecond pulse duration, and 1,200 mW of power.[1,2] Forty to 45 applications were placed 360 degrees around the corneoscleral limbus, which was slightly greater than the number used previously in performing Nd:YAG transscleral cyclophotocoagulation.[3]

Patients were reexamined at one and three hours after the operation with slit-lamp biomicroscopy and Goldmann applanation tonometry to observe for complications of the procedure. Patients were instructed to use prednisolone acetate 1% four times a day, as well as atropine 1% eyedrops twice a day in the operated-on eye and to continue their usual treatment for glaucoma.

The next morning patients underwent an ocular examination which included slit-lamp biomicroscopy, Goldmann applanation tonometry, inspection of the ocular adnexa, and ophthalmoscopy. A similar examination was performed thereafter at one week as well as one, three, and six months postoperatively. The dosages of prednisolone acetate 1% and atropine were tapered and discontinued as the postoperative ocular inflammation resolved. The number of glaucoma medications was reduced if the intraocular pressure decreased sufficiently.

Preoperative data evaluated in this study included age, gender, race, eye to be operated on, glaucoma diagnosis, Snellen visual acuity, results of Goldmann applanation tonometry, number of glaucoma medications prescribed, and reason for the procedure.

Postoperative data evaluated at six months included Snellen visual acuity, results of Goldmann applanation tonometry, number of glaucoma medications prescribed, and whether the procedure was successful. Success was defined as relief of pain in patients with no light perception or an intraocular pressure of 21 mm Hg or less without a change in Snellen visual acuity in patients with vision. Only data from a single laser treatment session were included in this report. Also noted were any complications in the operated-on eye during the six-month follow-up period.

Statistical differences between the preoperative and the postoperative intraocular pressures at each clinic visit were evaluated using a paired *t*-test. In patients whose eyes were reoperated on between three and six months after the initial procedure the last intraocular pressure measured before a second operation was used as a six-month measurement.

Results

Fourteen patients (14 eyes) with an average age of 69.9 ± 13 years (range, 38 to 84 years) were included in this study. Eight patients were men and six were women; 12 were black and two were white. Seven of the treated eyes were right eyes and seven were left eyes.

Nine patients had a preoperative diagnosis of chronic open-angle glaucoma, three had neovascular glaucoma, one had increased intraocular pressure associated with fungal endophthalmitis, and one had increased intraocular pressure after penetrating keratopathy. Diode laser cyclophotocoagulation was performed in ten patients to preserve vision and in four patients to relieve pain.

The preoperative and six-month postoperative intraocular pressures, visual acuities, and number of medications, as well as whether the laser treatment was a success or failure, were analyzed (Table). The mean preoperative intraocular pressure decreased from 34.8 ± 13 mm Hg preoperatively to 24.3 ± 18 mm Hg six months postoperatively. The average number of glaucoma medications prescribed per patient decreased from 2.2 preoperatively to 1.4 at six months postoperatively. Six patients had a postoperative reduction in the number of medications and none required an increase. Laser treatment was considered successful according to the criteria in ten of the 14 patients. This included three of four patients in whom pain was relieved and seven of ten patients in whom intraocular pressure was controlled to less than 21 mm Hg with no decrease in visual acuity.

The mean preoperative and postoperative intraocular pressures were determined at each clinic visit (Fig. 1). The postoperative change in intraocular pressure was statistically significant at each intraocular pressure measurement to $P > .005$.

Complications included mild uveitis and conjunctival burns (Fig. 2) in each patient. Ocular pain developed in one patient and a transient intraocular pressure increase greater than 10 mm Hg on the day of the operation was observed in one patient. No patient had visual acuity loss, hypotony, or phthisis bulbi.

The treatments of four patients were consid-

TABLE

EFFECT OF A SINGLE SEMICONDUCTOR DIODE TRANSSCLERAL CYCLOPHOTOCOAGULATION TREATMENT IN PATIENTS WITH GLAUCOMA

	PREOPERATIVE DATA			POSTOPERATIVE DATA			
PATIENT NO.	INTRAOCULAR PRESSURE (MM Hg)	VISUAL ACUITY	NO. OF MEDICATIONS	INTRAOCULAR PRESSURE (MM Hg)	VISUAL ACUITY	NO. OF MEDICATIONS	TREATMENT SUCCESS
1	58	N.L.P.	0	44	N.L.P.	0	Yes
2	42	N.L.P.	2	15	N.L.P.	2	Yes
3	22	H.M.	2	9	H.M.	2	Yes
4*	40	H.M.	2	20	H.M.	1	Yes
5	24	H.M.	4	14	H.M.	3	Yes
6	44	N.L.P.	0	37	N.L.P.	0	Yes
7	23	C.F.	3	12	C.F.	1	Yes
8	31	C.F.	2	24	C.F.	2	No
9	25	C.F.	3	18	C.F.	3	Yes
10	48	20/150	3	25	20/150	3	No
11	28	C.F.	3	7	C.F.	0	Yes
12	20	C.F.	3	16	C.F.	0	Yes
13	54	N.L.P.	2	72	N.L.P.	0	No
14	24	20/80	2	26	20/80	2	No

*Intraocular pressure was measured with a pneumotonometer and was not included in data analysis. N.L.P. indicates no light perception; H.M. indicates hand motion; C.F. indicates counting fingers.

ered failures according to study criteria because of inability to control intraocular pressure or persistent pain. Patient 8 had neovascular glaucoma and had an increased intraocular pressure despite previous cyclocryotherapy. Her intraocular pressure was initially controlled after diode laser transscleral cyclophotocoagulation for three months postoperatively, after which her intraocular pressure again increased to preoperative levels. Her intraocular pressure currently is controlled after repeat cyclocryotherapy. Patient 10 had an initial decrease in intraocular pressure from 42 mm Hg to 15 mm Hg for three months after diode cyclophotocoagulation. However, her pressure increased to 25 mm Hg, for which she underwent a repeat diode treatment, which currently controls her intraocular pressure. Patient 13 underwent cyclophotocoagulation to relieve pain. He discontinued the use of both his glaucoma medica-

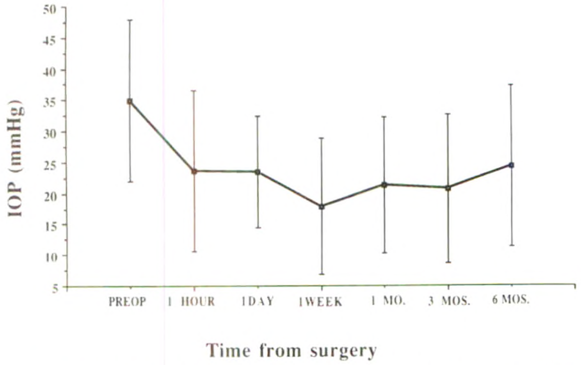

Fig. 1 (Hennis and Stewart). Pre- and postoperative intraocular pressures (means and standard deviations) in patients treated with semiconductor diode transscleral cyclophotocoagulation; IOP indicates intraocular pressure.

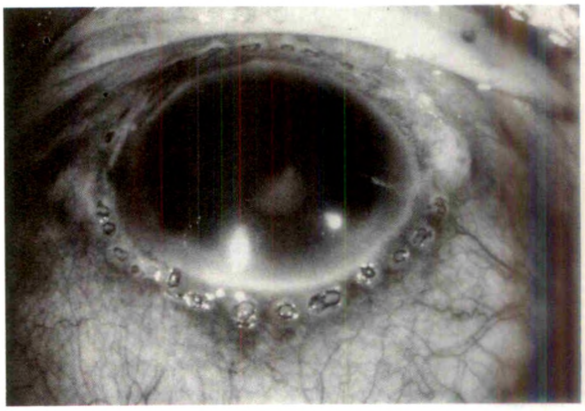

Fig. 2 (Hennis and Stewart). Clinical photograph showing conjunctival burns after semiconductor diode transscleral cyclophotocoagulation.

tions postoperatively and had a postoperative intraocular pressure increase from 54 to 72 mm Hg six months over the preoperative levels with persistent ocular pain. Patient 14 had an initial decrease in intraocular pressure one week postoperatively that increased to preoperative levels three months later.

Discussion

When indicated, laser transscleral cyclophotocoagulation has been shown to be a useful cyclodestructive procedure to reduce the intraocular pressure in patients with glaucoma. Although the ruby and the argon-krypton lasers[4,5] have been used previously, the Nd:YAG laser recently has been the instrument usually used for performing transscleral cyclophotocoagulation. The Nd:YAG laser has reduced intraocular pressure by 45% to 65% in patients with aphakic or neovascular glaucoma, or after penetrating keratoplasty.[3,6-8]

In our study we used a portable semiconductor diode laser with a slit-lamp delivery system to perform noncontact transscleral cyclophotocoagulation in patients with glaucoma. Compared to the Nd:YAG laser, the semiconductor diode laser has the potential advantage of better melanin absorption and consequently less use of energy to perform cyclophotocoagulation.[9]

In previous studies of cadaver eyes, ciliary process blanching and shrinkage with diode laser cyclophotocoagulation have been described that were similar to lesions produced with the Nd:YAG laser.[1,2,10,11] Diode laser transscleral cyclophotocoagulation also reduced the intraocular pressure to an extent similar to that of the Nd:YAG laser for the first six postoperative weeks in rabbits.[12]

Our study showed that semiconductor diode transscleral cyclophotocoagulation causes a statistically significant decrease ($P > .005$) in the intraocular pressure in patients with glaucoma. Most of the intraocular pressure response was observed within the first postoperative week. Diode laser transscleral cyclophotocoagulation was conveniently performed as a slit-lamp attachment in an outpatient setting.

However, despite a statistical decrease in the mean intraocular pressure, the results were inconsistent among individuals. Some patients maintained an adequate ocular hypotensive effect, whereas in others the pressure became uncontrolled after the first postoperative month. All reasons for treatment failure were uncertain. With this commercially available instrument, the defocusing procedure using a millimeter rule probably was imprecise. Additionally, most laser applications made no apparent external tissue alteration by which to judge accuracy. Also, the available wattage on the Microlase laser was well below the 4 to 6 J generally used for Nd:YAG transscleral cyclophotocoagulation. These factors may have contributed to the intermittent failure of this procedure.

Complications included mild uveitis and conjunctival burns at the site of the laser applications in each patient. The uveitis resolved within a week after treatment with topical administration of prednisolone acetate 1% four times a day. The conjunctival burns appeared as a blanched pit with a brown border and usually resolved within several days postoperatively. One patient suffered mild ocular pain from the diode laser cyclophotocoagulation for up to one week postoperatively.

This study suggested the use of the semiconductor diode laser to perform transscleral cyclophotocoagulation in a reasonably safe, comfortable, and effective manner. Treatment efficacy may be improved by development of a more precise focusing mechanism (for example, contact probe and an automatic defocus built into the laser) and slightly increased wattage capability.

This study did not compare diode laser transscleral cyclophotocoagulation to other cyclodestructive techniques. Also, the potential benefit of repeat treatment with the diode laser was not explored. Further evaluation is needed to confirm the clinical usefulness of diode laser transscleral cyclophotocoagulation and the factors that will determine its most efficient use.

ACKNOWLEDGMENT

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References

1. Hennis, H. L., Assia, E., Stewart, W. C., Legler, U. F. C., and Apple, D. J.: Transscleral cyclophotocoagulation using a semiconductor diode laser in cadaver eyes. Ophthalmic Surg. 21:274, 1991.

2. Assia, E. I., Hennis, H. L., Stewart, W. C., Legler, U. F. C., Carlson, A. N., and Apple, D. J.: Comparison of Nd:YAG and diode transscleral cyclophotocoagulation and cyclocryotherapy. Invest. Ophthalmol. Vis. Sci. 32:2774, 1991.

3. Stewart, W. C.: Clinical Practice of Glaucoma. Thorofare, New Jersey, Slack, Inc., 1990, p. 399.

4. Beckman, H., and Waeltermann, J.: Transscleral ruby laser cyclocoagulation. Am. J. Ophthalmol. 98:788, 1984.

5. Peyman, G. A., Conway, M. D., Raichand, M., and Lin, J.: Histopathologic studies on transscleral argon-krypton photocoagulation with an exolaser probe. Ophthalmic Surg. 15:496, 1984.

6. Klapper, R. M., Wandel, T., Donnenfeld, E., and Perry, H. D.: Transscleral neodymium:YAG thermal cyclophotocoagulation in refractory glaucoma. A preliminary report. Ophthalmology 95:719, 1988.

7. Badeeb, O., Trope, G. E., and Mortimer, C.: Short-term effects of neodymium:YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma. Br. J. Ophthalmol. 72:615, 1988.

8. Hampton, C., Shields, M. B., Miller, K. N., and Blasini, M.: Evaluation of a protocol for transscleral neodymium:YAG cyclophotocoagulation in one hundred patients. Ophthalmology 97:910, 1990.

9. Sigelman, J.: Retinal Diseases. Pathogenesis, Laser Therapy, and Surgery. Boston, Little, Brown and Company, 1984, p. 77.

10. Fankhauser, F., van der Zypen, E., Kwasniewska, S., Rol, P., and England, C.: Transscleral cyclophotocoagulation using a neodymium YAG laser. Ophthalmic Surg. 17:94, 1986.

11. Hampton, C., and Shields, M. B.: Transscleral neodymium:YAG cyclophotocoagulation. A histologic study of human autopsy eyes. Arch. Ophthalmol. 106:1121, 1988.

12. Schuman, J. S., Jacobson, J. J., Puliafito, C. A., Noecker, R. J., and Reidy, W. T.: Experimental use of semiconductor diode laser in contact transscleral cyclophotocoagulation in rabbits. Arch. Ophthalmol. 108:1152, 1990.

OPHTHALMIC MINIATURE

As I drove toward town I was thinking about that ancient and honorable bit of homely psychology, that myth of the ripeness of cataracts. The lens capsule can be removed as soon as it begins to get cloudy. But postoperative vision with corrective lenses is a poor resource at best, compared with normal sight. So the ripeness they speak of is the psychological ripeness of the patient, a time of diminishing vision which lasts long enough, and gets bad enough, so that the postoperative vision is, by comparison, a wonder and a delight. The patient is happy because the basis of comparison has changed.

John D. MacDonald, *The Long Lavender Look*
New York, Ballantine Books, 1970, pp. 84–85

Ocular Motility Anomalies in Developmental Misdirection of the Optic Chiasm

JillAnne W. McCarty, M.D., Joseph L. Demer, M.D., Laura A. Hovis,
and Marc R. Nuwer, M.D.

A 35-year-old normally pigmented man underwent monocular hemifield visual-evoked potential examinations that indicated a lack of normal decussation of nasal paramacular retinogeniculate fibers in the optic chiasm. We studied effects of this anomaly on ocular motility using electro-oculography and the magnetic search-coil technique. The patient exhibited horizontal congenital nystagmus with a predominantly positive exponential waveform. Horizontal smooth pursuit and optokinetic nystagmus were consistently reversed, independent of eye position in the orbit. Vertical tracking was uniformly normal. Horizontal vestibulo-ocular reflexes recorded in the dark during passive rotation exhibited normal gain and phase, whereas rotation recorded in the light reduced gain. Although active head movements reversed horizontal vestibulo-ocular reflexes, vertical vestibulo-ocular reflexes in light and darkness were normal. Our study suggested an association between a lack of normal decussation of retinal fibers in the optic chiasm, and reversed visual tracking and congenital nystagmus.

EXCESSIVE DECUSSATION of retinal fibers through the optic chiasm is well documented in albinism. Temporal retinal fibers that would normally project ipsilaterally have been shown to cross in the chiasm along with nasal retinal fibers, providing each hemisphere with a predominantly monocular input from the contralateral eye. This finding has been described anatomically in several species of albino animals as well as in humans.[1,2] Visual-evoked potential asymmetries corroborating this anomalous decussation have also been reported clinically in various types of ocular and oculocutaneous albinism.[3-6]

Visual tracking defects and congenital nystagmus are also typical of albinism. Reversed smooth pursuit and optokinetic nystagmus abnormalities have been described.[7,8] It has been suggested that a reversed afferent signal from retinal ganglion cells could mediate the reversed tracking seen in this condition,[8-10] and may even be responsible for nystagmus.[11,12]

Axon fibers from ganglion cells in the nasal hemiretina normally decussate in the optic chiasm. Although failure of this decussation has not been previously reported in humans, a breed of dogs with congenital nystagmus that is achiasmatic and has no decussation of retinogeniculate fibers has recently been described.[13] A report of two patients with congenital nystagmus from one family who had asymmetric, full-field, visual-evoked potentials suggested a possible decussation anomaly in nonalbino congenital nystagmus.[14] An abnormal lack of decussation of retinal fibers in the optic chiasm may cause ocular tracking anomalies and congenital nystagmus. We conducted ocular motility studies in a normally pigmented man with congenital nystagmus who had visual-evoked potential evidence of failure of nasal paramacular fibers to decussate in the optic chiasm.

Case Report

A 35-year-old white man with horizontal congenital nystagmus underwent routine exam-

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ination. The patient had compound myopic astigmatism with a best-corrected visual acuity of R.E.: 20/30 and L.E.: 20/40. He had mild amblyopia in the left eye and small-angle esotropia. Ductions and versions were unremarkable. The patient had no stereoscopic perception. Visual fields were full bilaterally, as determined by Octopus perimetry. Slit-lamp examination documented normal iris pigment without transillumination defects. Biomicroscopy and indirect ophthalmoscopy disclosed normal pigmentation.

Material and Methods

Visual-evoked potential testing was performed using both full-field and hemifield stimulation with a black-and-white checkerboard pattern. Pattern reversal occurred at two per second. The pattern was 12 degrees wide and tall, with 50 arc-minute square checks. For hemifield testing, the fixation point was placed 1.5 cm to one side of the screen. Each eye was tested separately. Recordings were taken from both lateral occipital and posterior temporal regions. The midoccipital electrode was located 5 cm above the inion in the midsagittal plane, and the electrodes that were designated left and right occipital and left and right temporal were 5 and 10 cm lateral to the midoccipital electrode, respectively. The midparietal electrode was located 10 cm above the inion, and the electrodes that were designated left and right parietal and left and right lateral were located 5 and 10 cm lateral to the midparietal electrode, respectively. The reference was a frontal midline electrode, 12 cm above the nasion. Filters were 1 to 1,000 Hz. Signal averaging of 400 reversals of each visual presentation was used to reduce interference from nonevoked electroencephalographic activity.

The patient's eye movements were recorded by using two different techniques after written informed consent was obtained. For direct current electro-oculography, electrodes were placed on the skin at the medial and lateral canthi of each eye to record horizontal eye movements, as well as above and below one eye to detect blinks. After amplification and filtering over a bandwidth of 0 to 43 Hz, electro-oculographic potentials were displayed on a multichannel polygraph and were digitized for computer analysis.[15] This relatively noninvasive technique is adequate for prolonged testing of horizontal eye movements.

Magnetic search-coil recordings were performed for adequate analysis of vertical eye movements and for higher resolution studies of horizontal eye tracking. This technique entails placement on the anesthetized eye of an annular silicone suction contact lens into which an induction coil of wire has been embedded.[16] When placed in an appropriate external magnetic field, the induced electric voltage in the search coil can be electronically decoded to measure the horizontal and vertical position of the eye.[17] Use of the magnetic search coil is the best technique available for measurement of both horizontal and vertical eye movements,[18] but testing must be limited to about 30 minutes to avoid corneal irritation.

Each technique was calibrated for saccadic eye movements between targets of known eccentricities. For testing of saccades, the patient fixated a projected laser spot that was deflected pseudorandomly by a mirror galvanometer under computer control. To test smooth pursuit, the laser target was deflected sinusoidally. Full-field optokinetic nystagmus was tested for sinusoidal and constant velocity rotations of a vertically striped curtain surrounding the patient and rotated by a servomotor under computer control. Small-field optokinetic nystagmus was evoked with a handheld drum. Passive horizontal vestibulo-ocular reflexes were tested in total darkness for sinusoidal, whole-body rotations about a vertical axis at multiple frequencies spanning the range from 0.0125 through 1.25 Hz. Active vestibulo-ocular reflexes were tested in darkness during voluntary, sinusoidal head movements made by the patient in synchrony with an audible tone the pitch of which was modulated by a laboratory computer; both horizontal and vertical head movements were tested. For both passive and active head movements, visual-vestibular interaction was tested in normal room illumination of the clinical laboratory environment.

For eye movement data analysis, eye and stimulus velocities were obtained from measured position signals using analog and digital differentiation and were plotted using conventional techniques.[19] When relevant, the gain of each type of eye movement was computed as the ratio of slow-phase eye velocity response divided by stimulus velocity. Magnetic resonance imaging studies were performed in the coronal and axial planes at 0.3 T, with particular attention to the optic chiasm.

Results

Recording of visual-evoked potentials was attempted during monocular stimulation of only the nasal or temporal hemifield in each eye. No consistent responses were recordable from the right eye, or from the right (nasal) hemifield of the left eye. Visual-evoked potentials during stimulation of the left hemifield of the left eye were recorded (Fig. 1). The overall amplitude of the visual-evoked potential response was attenuated from the normal amplitude by an order of magnitude, a finding also noted in albinos.[5] Despite the small amplitudes, the P100 and P135 potentials were reproducibly seen on two separate test repetitions. Temporal field reception occurring on nasal retina would normally project to contralateral visual cortex, and produce a P135 peak (shown as a negative peak) largest over the contralateral (right) occipital scalp. In our patient, such stimulation actually produced a P135 peak at the ipsilateral (left) occiput. Likewise, the P100 peak, which is recorded from scalp contralateral to the stimulated occipital cortex, was repeatedly larger over the contralateral (right) occiput. This finding suggested a decrease in the proportion of nasal retinal fibers that decussated in the optic chiasm.

Magnetic resonance imaging studies disclosed a normal gross optic chiasm, with no lesions or hypoplasia noted in direct coronal and axial cuts (Fig. 2). The patient's spontaneous eye movements in the light were systematically recorded using electro-oculography (Fig. 3). Because the eye movements were conjugate, only recordings from the right eye are depicted. Spontaneous nystagmus was variably present, depending on direction of gaze and which eye was viewing. The overall waveform of the slow phase was mostly positive exponential, consisting of an increasing-velocity slow eye movement succeeded by a saccade. In primary gaze, the patient exhibited a null of nystagmus. When the right eye was covered, the nystagmus intensity in primary position increased, but the pattern was not typical of latent nystagmus. No spontaneous nystagmus was observed in darkness.

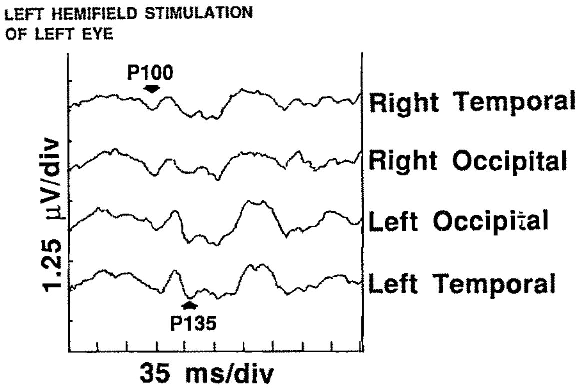
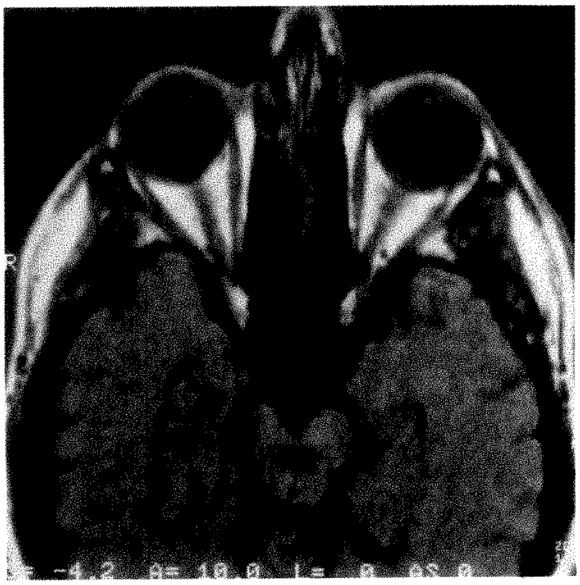


Fig. 1 (McCarty and associates). Visual-evoked potential recording of P100 and P135 peaks. Positive peaks correspond to downward deflections.

The patient's horizontal pursuit of a projected laser spot moving sinusoidally was recorded by the search-coil technique (Fig. 4). Although the patient's average eye position approximated the target position, it was achieved by saccades, rather than smooth eye movements. The patient's smooth pursuit eye movements were in the opposite direction of the target movement. The direction of the slow phase was not dependent merely on the position of the eye in the orbit, but also on the direction of target motion. For example (Fig. 4, short arrow), at a position 10 degrees to the left of primary, slow tracking eye movements for target motion at 0.2 Hz were to the left only when the target was moving to the right. At this same position (Fig. 4, long arrow), slow phase movements were to the right when target motion was to the left. These waveforms were therefore not a function of gaze angle. The abnormal horizontal pursuit was in contrast to the observed normal vertical pursuit (Fig. 5). At the higher frequency of 0.4 Hz, horizontal pursuit, although still reversed, became more disorganized. With a vertically directed target, eye position was observed to follow more smoothly, with minimal correcting saccades.

Optokinetic nystagmus was also reversed during horizontal stimulation, and was illustrated in search-coil recordings (Fig. 6). Rotation of the striped drum in either direction resulted in slow movements (tracking) in the opposite direction, with corrective quick phases in the direction of target motion. This was the reverse of the normal response, in which the slow phase tracks the target and resetting quick phases are opposite. However, the reversed optokinetic nystagmus cannot be caused by



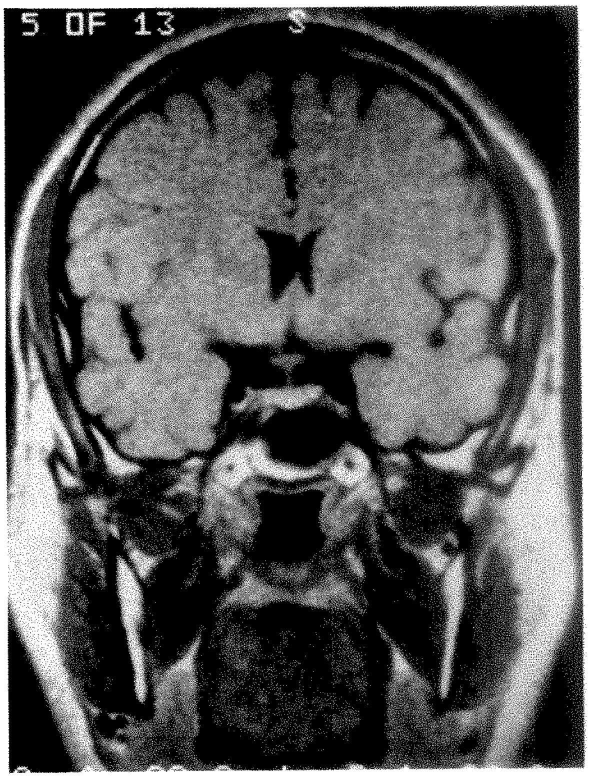


Fig. 2 (McCarty and associates). Magnetic resonance images of axial view (left) and coronal view (right) of optic chiasm of patient. The coronal view shows a grossly normal optic chiasm.

dependence of the spontaneous nystagmus waveform on orbital position, because average orbital position was nearly constant in the record (Fig. 6). The slow phases of horizontal optokinetic nystagmus were not linear, but instead were positive exponential, similar to the patient's baseline congenital nystagmus at 15 degrees to the right or left (Fig. 3). This was in contrast to the linear sawtooth-shaped waveforms with stable velocity that are seen in a normal optokinetic nystagmus. Vertical rotation of the drum (Fig. 7) produced the normal smooth tracking in the direction of drum rotation with corrective quick phases back toward primary gaze.

Horizontal and vertical saccadic eye move-

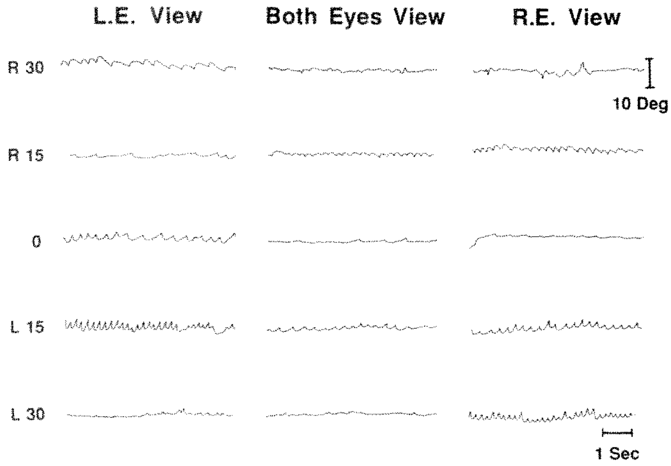


Fig. 3 (McCarty and associates). Spontaneous eye movements of the right eye recorded by electro-oculography. Target positions indicated are primary gaze (0), and 15 and 30 degrees to the right (R15, R30) and left (L15, L30) of primary position.

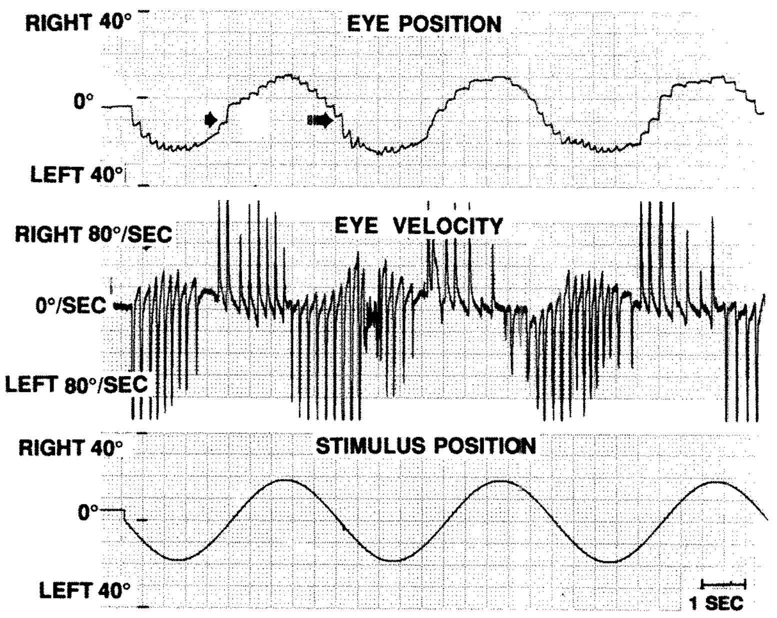


Fig. 4 (McCarty and associates). Horizontal pursuit recorded by magnetic search-coil technique. Movement to the right is recorded as up, movement to the left as down, with primary gaze in center (0). Short arrow indicates eye movements at 10 degrees left of primary position when target was moving to the right; long arrow indicates eye movements at same location (10 degrees left of primary position) when target was moving to the left.

ments exhibited normal trajectories, and the relationship between saccadic amplitude and peak velocity was normal.

Slow-phase eye velocity during passive sinusoidal rotation in the horizontal plan was recorded (Fig. 8, top). The response in darkness is called the vestibulo-ocular reflex, and is characterized by sinusoidal variation in eye velocity in roughly the opposite direction of head velocity. This is appropriate to stabilize the retinal images of fixed objects during head motion. At the frequency illustrated, the gain achieved by the patient (0.76) is the same as that obtained for normal subjects in our laboratory.

The visual vestibulo-ocular reflex was tested during similar rotation in light (Fig. 8, bottom). In contrast to the normal performance in darkness, both the sinusoidal waveform and gain (0.54) were compromised in the light. This disclosed visual input, rather than vestibulo-ocular reflex enhancement, was the cause for disruption in this patient. The horizontal vestibulo-ocular response and visual vestibulo-ocular response for active head rotation were

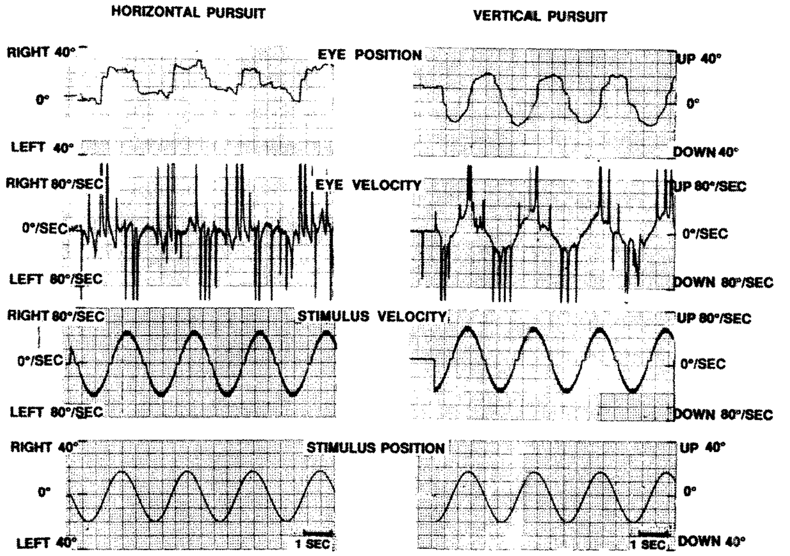


Fig. 5 (McCarty and associates). Horizontal and vertical pursuit movements of the right eye as recorded by the magnetic search-coil technique.

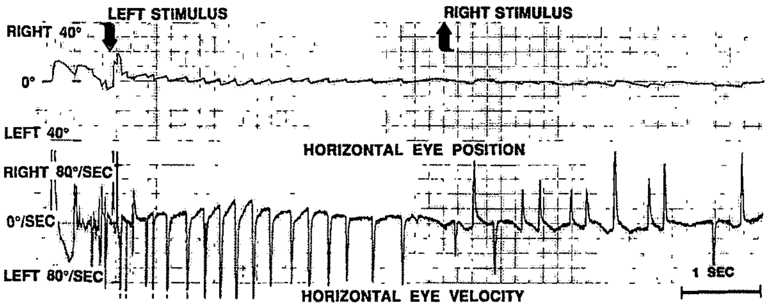


Fig. 6 (McCarty and associates). Horizontal optokinetic nystagmus recorded by magnetic search-coil technique for the right eye. Drum rotation to the left is indicated as left stimulus (arrow pointing down); drum rotation to the right is indicated as right stimulus (arrow pointing up).

reversed in direction, so that eyes tracked in the same direction as the head. Vertical vestibulo-ocular reflexes and visual vestibulo-ocular reflexes exhibited normal gain and direction when tested during active sinusoidal head movements at 0.4 to 1.6 Hz.

Discussion

Retinal nerve fiber misdirection in the optic chiasm has been suggested as the cause of congenital nystagmus[11,12] and associated visual tracking abnormalities in albinos.[8-10] We provided an additional example of a relationship between anomalous decussation of retinal nerve fibers through the chiasm and reversed visual tracking. In this nonalbino patient with congenital nystagmus, we found evidence that a failure of nasal retinal fiber decussation, in contrast to the excessive temporal retinal decussation seen in albinos (Fig. 9), can have a role in reversed visual tracking and in the manifestation of congenital nystagmus. Stimulation of the temporal hemifield (and thus the nasal hemiretina) of the patient's left eye activated the ipsilateral occipital cortex, whereas hemifield visual-evoked potentials were nonrecordable in the opposite hemifield and for the fellow eye. Although this indicated nondecussation of the retinogeniculate projection from the nasal hemiretina of the left eye, the reduced evoked potential amplitude and lack of potentials in other hemifields were also suggestive of anomalous retinocortical projections. A disruption in the timing and symmetry of retinocortical projections might be expected with extensive chiasmal misrouting.

Our findings corroborated a theoretic model for congenital nystagmus that was previously proposed by Optican and Zee.[12] According to the model, the increasing-velocity waveform of slow eye movements seen in congenital nystagmus can occur as a result of a reversed afferent visual signal mediating velocity feedback. That is, as the eyes drift off target, direction-sensitive retinal fibers projecting abnormally through the chiasm produce a reversed afferent direction sign. This causes the eyes to accelerate in the wrong direction, away from the target, depending on the velocity of the initial drift. The eyes continue to run away from the target with increasing velocity as inappropriately reversed velocity feedback persists. Ultimately, a resetting saccade occurs because of an intact position feedback system, and refoveates the target. The predictions of the Optican and Zee model conform closely to most congenital nystagmus waveforms characterized clinically.[20,21] Congenital nystagmus waveforms, as we also found, have typically consisted of an in-

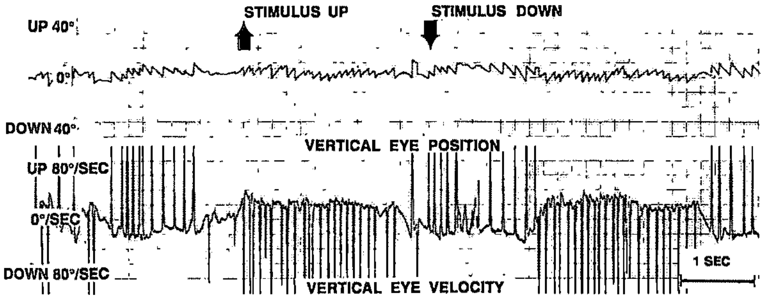


Fig. 7 (McCarty and associates). Vertical optokinetic nystagmus as determined by magnetic search-coil technique. Rotation of drum upward is indicated by stimulus up (arrow pointing up); drum rotation downward is indicated by stimulus down (arrow pointing down).

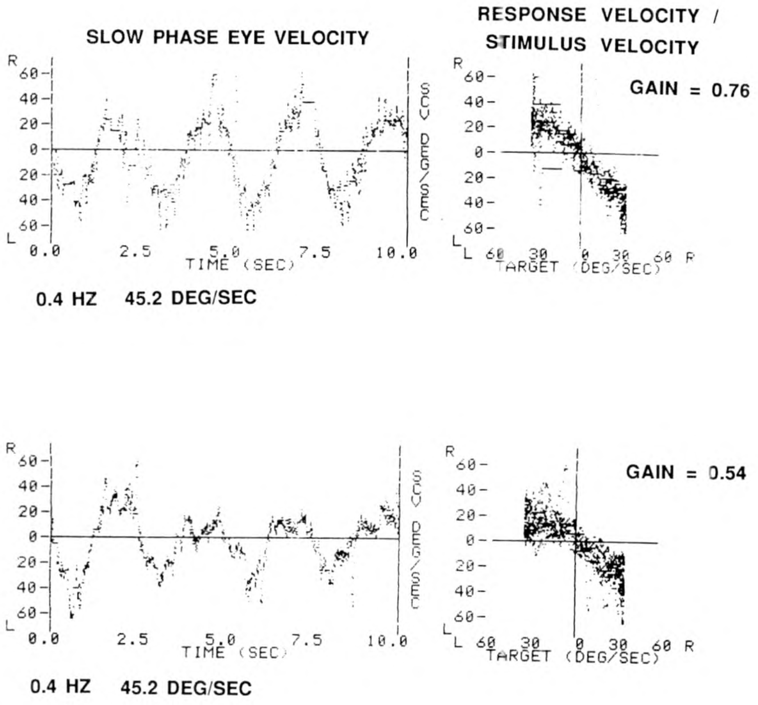


Fig. 8 (McCarty and associates). Passive vestibulo-ocular reflex recordings in total darkness at a frequency of 0.4 Hz. Top left, A composite of slow phase eye movement velocities over time. Top right, Gain is shown as the ratio of response velocity to stimulus velocity. Bottom, left and right, Passive visual vestibulo-ocular reflex recordings in ambient light, with slow phase eye movement velocities and gain as depicted in top of figure.

creasing-velocity slow eye movement away from the target succeeded by a foveating saccade that returns the eyes to the target.

Tracking abnormalities in congenital nystagmus, including reversed smooth pursuit[9,21] and defects in optokinetic nystagmus,[9,22-25] have been characterized previously. Saccades and vestibulo-ocular reflexes are usually normal. Additionally, visual vestibulo-ocular reflex studies have disclosed impairment rather than augmentation of the normal vestibulo-ocular reflex with visual input in congenital nystagmus.[9,23] Misdirection of retinal fibers in the chiasm would also account for these motility findings. Direction-sensitive retinal ganglion cells that cross in the chiasm to synapse in the contralateral nucleus of the optic tract in normal rabbits, evidently serving as the afferent link in the optokinetic reflex arc, have been identified.[26] This pathway is stimulated by target velocity rather than position. Anomalous projection of these retinal fibers to the ipsilateral nucleus of the optic tract could thus induce a reversed signal and reversed tracking. Hoffman[27] found that in human adults, both this contralateral subcortical and a bilateral cortical input to the nucleus of the optic tract govern optokinetic nystagmus movements, with the cortical afferent pathway being dominant. However, Hoffman[27] reported that the development of the cortical pathway is dependent on appropriate input from the subcortical (direct retinal) pathway. In congenital nystagmus, therefore, the subcortical direct retinal projection to the nucleus of the optic tract may retain its immature dominance and have an increased role in governing pursuit and optokinetic tracking eye movements.

Previous reports have argued that reversed optokinetic nystagmus seen in congenital nystagmus is not a true reversal of optokinetic nystagmus, but rather is the patient's baseline congenital nystagmus waveform somehow shifted to primary position by the optokinetic mystagmus stimulus.[9,22,24,25] These authors contended that single velocity (linear) waveforms

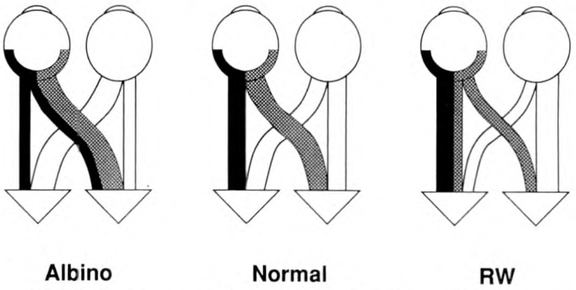


Fig. 9 (McCarty and associates). Schematic diagram of retinogeniculate projections via the optic chiasm in albino (left) and normal (middle) patients and in our patient (right).

are necessary to indicate truly reversed optokinetic nystagmus. We contended that such a criterion is not warranted. Obviously, a case in which the patient's typical congenital nystagmus waveforms continue unchanged with optokinetic stimulation, irrespective of stimulus direction, does not reflect reversed optokinetic nystagmus.[22] However, our patient's bidirectional slow wave responses reversed, depending only on target direction in the same orbital position, and were not present in primary position in the absence of the optokinetic stimulus. Such a response does demonstrate true reversed optokinetic nystagmus. In the reversed afferent feedback model of Optican and Zee,[12] reversed visual velocity feedback caused by chiasmal misrouting makes generation of a linear velocity slow tracking movement impossible. Instead, the optokinetic waveforms with a positive exponential slow phase as observed in our patient are predicted.

Congenital nystagmus waveforms are modified by a fixation attempt.[20] However, attempted fixation cannot be invoked as a trivial explanation for the reversed tracking observed in our study. The stimulus for optokinetic nystagmus covered the patient's entire visual field, not just the fovea, and during optokinetic nystagmus testing, no conscious attempt at fixation was made. Reversed pursuit that is independent of eye position has also been previously described in congenital nystagmus.[9] In a study that used an open-loop system to keep retinal slip constant, pursuit abnormalities persisted in a patient with congenital nystagmus.[28] These studies argued against a simple refoveation mechanism for reversed smooth pursuit movements in congenital nystagmus, again indicating a true reversal in the slow tracking system.

In agreement with previous reports,[9,23] the passive horizontal vestibulo-ocular reflex in our patient was essentially preserved, suggesting that passive vestibulo-ocular reflexes are calibrated independently of pursuit. Similar to previous findings in congenital nystagmus,[9,23] visual interaction disrupted rather than enhanced the vestibulo-ocular reflex. This paradoxic effect was intriguing because the vestibulo-ocular reflex, which induces short latency ocular movements compensatory for head movements even in complete darkness, is nevertheless subject to continuous calibration by vision during such movements in the light. During growth, aging, and in response to trauma, both the mechanical characteristics of the extraocular musculature and the neural apparatus subserving eye movements change. Through all these changes, vestibulo-ocular reflex gain remains close to 1.0. The nervous system must be detecting errors and constantly recalibrating the reflex. Gonshor and Melvill-Jones[29] first demonstrated the modifiability of vestibulo-ocular reflex gain by observing that people who wear Dove prism-reversing spectacles undergo a gradual decrease in vestibulo-ocular reflex gain, a finding that has been confirmed in animals.[30,31] Dove prisms reverse the normal relationship between head movement and the apparent motion of the visual environment, so that in the absence of a vestibulo-ocular reflex, the images of stationary objects on the retina would move in the same direction as the head, instead of in the opposite direction as normally occurs. It is believed that one of two factors signal the recalibration of the vestibulo-ocular reflex: either the direction and amount of image motion during head movement, or the visual pursuit effort used to reduce this image motion during head movement.[32] In either case, reversed horizontal pursuit tracking caused by the type of chiasmal misrouting observed in our patient would be expected to signal the vestibulo-ocular reflex to reduce vestibulo-ocular reflex gain or even to reverse the direction of the reflex altogether. Normal horizontal vestibulo-ocular reflex performance was therefore surprising in our patient. Presumably, the patient's vestibulo-ocular reflex was calibrated by neural mechanisms independent of retinal image motion and pursuit tracking.

Consistent with the functional segregation of central pathways subserving horizontal vs vertical eye movements, all ocular movements in the vertical plane were normal in our patient. The misrouting of the axons of horizontal motion-sensitive ganglion cells would not be expected to influence vertical eye movement reflexes, which are often completely normal in congenital nystagmus.[33]

The visual-evoked potential asymmetries in two other nonalbino patients with congenital nystagmus[14] suggested anomalous projection of retinal fibers through the optic chiasm in these patients. Another recent report[6] evaluated full-field, monocular, visual-evoked potentials in ten patients with congenital nystagmus, and found no visual-evoked potential asymmetries. A distinct topographic localization of retinal fibers important in reversed tracking and congenital nystagmus, with misrouting only for retinogeniculate axons subserving a limited region of the visual field, may exist. If so, evoked potentials averaged over the entire visual field might miss subtle local misrouting. A threshold number of fibers that decussate abnormally is necessary to detect an asymmetric, full-field, visual-evoked potential response, and this threshold may be higher than the number necessary to induce the tracking and eye movement anomalies observed in our study. Decussation abnormalities may be more specifically studied with hemifield paramacular visual-evoked potential stimulation. The report of a new animal model for congenital nystagmus that has no optic chiasm, and thus exhibits purely ipsilateral projection of retinal fibers,[13] supported the involvement of anomalous chiasmal direction of retinal fibers in the generation of reversed visual tracking and the induction of congenital nystagmus. Further functional studies of the afferent visual pathways in other patients with congenital nystagmus may be insightful.

References

1. Guillery, R. W., Okoro, A. N., and Witkop, C. J.: Abnormal visual pathways in the brain of a human albino. Brain Res. 96:373, 1975.
2. Giolli, R. A., and Creel, D. J.: The primary optic projections in pigmented and albino guinea pigs. An experimental degeneration study. Brain Res. 55:25, 1973.
3. Creel, D., Witkop, C. J., and King, R. A.: Asymmetric visually evoked potentials in human albinos. Evidence for visual system anomalies. Invest. Ophthalmol. 13:430, 1974.
4. Creel, D., O'Donnell, F. E., and Witkop, C. J.: Visual system anomalies in human ocular albinos. Science 201:931, 1978.
5. Jay, B., and Carroll, W.: Albinism. Recent advances. Trans. Ophthalmol. Soc. U.K. 100:467, 1980.
6. Apkarian, P., and Shallo-Hoffman, J.: VEP projections in congenital nystagmus. VEP asymmetry in albinism. A comparison study. Invest. Ophthalmol. Vis. Sci. 32:2653, 1991.
7. Demer, J. L., and Zee, D. S.: Vestibulo-ocular and optokinetic deficits in albinos with congenital nystagmus. Invest. Ophthalmol. Vis. Sci. 25:739, 1984.
8. Collewign, H., Winterson, B. J., and Dubois, M. F. W.: Optokinetic eye movements in albino rabbits. Inversion in anterior visual field. Science 199:1351, 1978.
9. Halmagyi, G. M., Gresty, M. A., and Leech, J.: Reversed optokinetic nystagmus (OKN). Mechanism and clinical significance. Ann. Neurol. 7:429, 1980.
10. Mein, J.: The asymmetrical optokinetic response. Br. Orthop. J. 40:1, 1985.
11. Guillery, R. W.: Normal and abnormal visual pathways. Trans. Ophthalmol. Soc. U.K. 99:352, 1979.
12. Optican, L. A., and Zee, D. S.: A hypothetical explanation of congenital nystagmus. Biol. Cybern. 50:119, 1984.
13. Williams, R. W., Garraghty, P. E., and Goldowitz, D.: A new visual system mutation. Achiasmatic dogs with congenital nystagmus. Soc. Neurosci. 17:187, 1991.
14. Meienberg, O., Hemphill, G., Rosenberg, M., and Hoyt, W. F.: Visually evoked response asymmetries in a family with congenital nystagmus. Possible evidence of abnormal visual projections. Arch. Neurol. 37:697, 1980.
15. Baloh, R. W., Langhofer, L., Honrubia, V., and Yee, R. D.: On-line analysis of eye movements using a digital computer. Aviat. Space Environ. Med. 51:563, 1980.
16. Collewign, H., van der Mark, F., and Jansen, T. C.: Precise recording of human eye movements. Vision Res. 15:447, 1975.
17. Robinson, D. A.: A method of measuring eye movement using a scleral search coil in a magnetic field. Inst. Elec. Electron. Engr. Trans. Biomed. Electron. 10:137, 1963.
18. Yee, R. D., Schiller, V. L., Lim, V., Baloh, F. G., Baloh, R. W., and Honrubia, V.: Velocities of vertical saccades with different eye movement recording methods. Invest. Ophthalmol. Vis. Sci. 26:938, 1985.
19. Demer, J. L., Holds, J. B., and Hovis, L. A.: Eye movements in essential blepharospasm. Am. J. Ophthalmol. 110:674, 1990.
20. Dell'Osso, L. F., and Daroff, R. B.: Congenital nystagmus waveforms and foveation strategy. Doc. Ophthalmol. 39:155, 1975.
21. Yee, R. D., Wong, E. K., Baloh, R. W., and Honrubia, V.: A study of congenital nystagmus. Waveforms. Neurology 26:326, 1976.
22. Yee, R. D., Baloh, R. W., and Honrubia, V.: Study of congenital nystagmus. Optokinetic nystagmus. Br. J. Ophthalmol. 64:926, 1980.
23. Yamazaki, A.: Abnormalities of smooth pursuit and vestibular eye movements in congenital jerk nystagmus. In Shimuzu, K. (ed.): Ophthalmology, Vol. 2. Amsterdam, The Netherlands, Excerpta Medica, 1979, p. 1162.
24. LeLiever, W. C., and Barber, H. O.: Observations on optokinetic nystagmus in patients with congenital nystagmus. Otolaryngol. Head Neck Surg. 89:110, 1981.
25. Abadi, R. V., Dickinson, C. M., and Lonas, M. S.: Inverted and asymmetrical optokinetic nystagmus. In Lennerstrand, G., Zee, D. S., and Keller, E. L. (eds.): Functional Basis of Ocular Motility Disorders. Oxford, Pergammon Press, 1982, p. 143.
26. Collewign, H.: Direction-selective units in the rabbit's nucleus of the optic tract. Brain Res. 100:489, 1975.
27. Hoffmann, K.-P.: Neural basis for changes of the optokinetic reflex in animals and men with strabismus and amblyopia. In Lennerstrand, G., von

Noorden, G. K., and Campos, E. C. (eds.): Strabismus and Amblyopia. Experimental Basis for Advances in Clinical Management. London, MacMillan Press, 1988, p. 89.

28. Optican, L. M., Zee, D. S., Chu, F. C., and Cogan, D. G.: Open loop pursuit in congenital nystagmus. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1983, p. 271.

29. Gonshor, A., and Melvill-Jones, G.: Plasticity in the adult human vestibulo-ocular reflex arc. Proc. Can. Fed. Biol. Sci. 14:11, 1971.

30. Melvill-Jones, G., and Davies, P.: Adaptation of cat vestibulo-ocular reflex to 200 days of optically-reversed vision. Brain Res. 103:551, 1976.

31. Miles, F. A., and Eighmy, B. B.: Long-term adaptive changes in primate vestibuloocular reflex. I. Behavioral observations. J. Neurophysiol. 43:1406, 1980.

32. Miles, F. A., and Lisberger, S. G.: Plasticity in the vestibulo-ocular reflex. A new hypothesis. Annu. Rev. Neurosci. 4:273, 1981.

33. Demer, J. L.: Vertical eye movements in congenital nystagmus. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, p. 816.

OPHTHALMIC MINIATURE

The pain began in his eyes just as he skirted a long clump of tangled ferns to reach a natural clearing between stands of trees. The rain started then, too, whipping down hard, stinging.

His eyes were burning, both of them. He squinted the jeep into the turn, gunning it through the long, narrow clearing. He brought his left hand up to rub his eyes, realizing it was a mistake when his lips and tongue began burning, too.

His hands were burning, also, as he pulled them away from his face, his vision blurring, the pain like hot needles jammed into his eyes. He saw smoke rising from his hand.

Mike McQuay, *Puppetmaster*
New York, Bantam Books, 1991, pp. 477–478

EDITORIALS

Praise for my Predecessor and a New Editorial Board for the Nineties

Michael A. Kass

> It is impossible to dissociate language from science or science from language, because every natural science always involves three things: the sequence of phenomena on which the science is based; the abstract concepts which call these phenomena to mind; and the words in which the concepts are expressed. To call forth a concept a word is needed; to portray a phenomenon, a concept is needed. All three mirror one and the same reality.
>
> ANTOINE-LAURENT LAVOISIER
> *Traité elémentaire de chemie*, 1789

This issue of THE JOURNAL marks the end of an era as Frank W. Newell steps down as editor. I now am the seventh editor of THE JOURNAL since its founding in 1884. The previous editors and their terms of service are as follows: Adolf Alt, 1884–1917; Edward Jackson, 1918–1927; William H. Crisp, 1928–1931; Lawrence T. Post, 1931–1941; Derrick T. Vail, 1941–1965; Frank W. Newell, 1965–1991.

I wish to praise the dedication and commitment of my predecessor. Frank W. Newell began his association with THE JOURNAL over 46 years ago as an author and reviewer. He served for nine years as a member of the Editorial Board, six years as editor of the Research Section, two years as associate editor, and 26 years as editor-in-chief. The quotation from Lavoisier, which is the frontispiece of this editorial, summarizes Frank's untiring efforts to achieve journalistic excellence. Frank has steadfastly promoted the careful observation of phenomena, the development of abstract concepts to explain normal function and disease, and the proper choice of language to summarize these observations and concepts. At all times he has insisted on the highest scientific, medical, and literary standards for THE JOURNAL. Under his guidance, THE JOURNAL has become one of the most respected publications in all of medicine. I think it is fair to say that to many readers and contributors, Frank is THE JOURNAL. Frank's advice has been, and will continue to be, invaluable in his role as publisher.

I invite the readers to review THE JOURNAL masthead, which lists the new Editorial Board. There are eight new members of the Editorial Board and six members who have previously served on the Board. This distinguished group is characterized by scholarship, experience, accomplishment, and integrity. With the help of the Board and hundreds of skilled reviewers, the editor can call on experts in all clinical and research areas of medicine relevant to ophthalmology.

Thomas M. Aaberg will continue as senior associate editor of THE JOURNAL. His experience and sage advice will be of great service to the new editor. Ronald M. Burde, an ophthalmologist with wide-ranging interests in medicine and science, will succeed me as abstract editor. I served in that position for one year after the untimely death of David Shoch. Mark Mannis, a physician with an extensive background in ophthalmology and literature, succeeds H. Stanley Thompson as book review editor. Stan Thompson, who has been an exemplary book review editor, will remain on the Editorial Board.

THE JOURNAL will maintain its office in Chicago under the able direction of Frank W. Newell, publisher, and Mary L. Borysewicz, executive managing editor. This office will be responsible for the manuscript preparation, printing, distribution, subscriptions, and advertising of THE JOURNAL. I will be responsible for review and selection of manuscripts.

Despite the proliferation of ophthalmic subspecialties and subspecialty publications, THE JOURNAL will continue to publish material on all facets of ophthalmology. These will include original observations, case series, clinical trials, letters, editorials, perspectives, and laboratory reports relevant to clinical ophthalmology.

I close this editorial with two promises to our authors and our readers. To authors, I promise the continuation of fair, expert peer review and rapid publication. To readers, I promise the best scientific and clinical published material in ophthalmology. On many occasions I heard Frank Newell state, "We must never forget that our primary obligation is to the reader." By serving the reader, THE JOURNAL best serves medicine, science, and ophthalmology.

LETTERS TO THE JOURNAL

Lens-induced Endophthalmitis After Nd:YAG Laser Iridotomy

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Alan Lessner, M.D.,
Stacia H. Goldey, M.D.,
and Mark Sherwood, M.D.

Departments of Ophthalmology (C.E.M., A.L., S.H.G., M.S.) and Pathology (C.E.M.), University of Florida.

Inquires to Alan Lessner, M.D., Dept. of Ophthalmology, University of Florida, Box J-284, JHMHC, Gainesville, FL 32610.

Nd:YAG laser iridotomy is an effective and safe means of treating pupillary block glaucoma. Few serious intraocular complications have been reported.[1-4] We treated a patient with severe lens-induced endophthalmitis after Nd:YAG laser iridotomy.

A 44-year-old woman had severe pain in her left eye for two months after two Nd:YAG laser iridotomies. She had been blind (no light perception) in that eye from chronic closed-angle glaucoma for almost 15 years. A mature cataract had been present for at least five years. Since the eye was blind and previously comfortable, increased intraocular pressures (usually in the 20s and low 30s) had been treated conservatively with a variety of topical medications for several years. The eye had never undergone any surgical procedures until the iridotomies, which were performed when the intraocular pressure rose to 48 mm Hg and iris bombé was observed on examination. We confirmed that the sites of the Nd:YAG laser iridotomies were at 12 and 3 o'clock with the treating ophthalmologist, but other details of the procedure were not recorded. The day after laser treatment intraocular pressure fell into the 20s and a fibrinous iritis was observed; hourly, topical treatment with corticosteroids was prescribed. Similar finding were seen after one week. The left eye became progressively painful, tender, and injected over the next seven weeks.

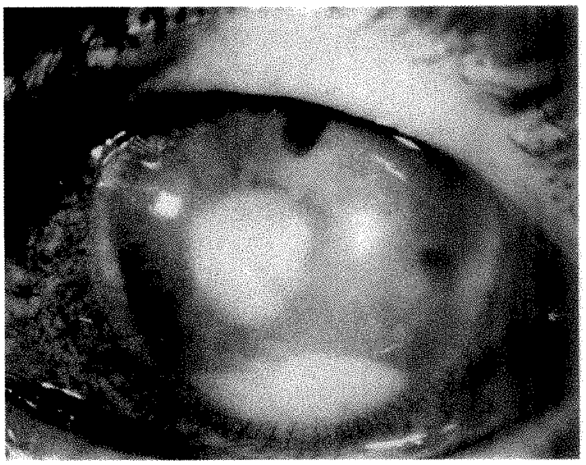

Fig. 1 (Margo and associates). The left eye eight weeks after Nd:YAG laser iridotomies at 12 and 3 o'clock shows a hypopyon and numerous large keratic precipitates. White flocculent material obscures the pupil. The lens cannot be visualized through either iridotomy.

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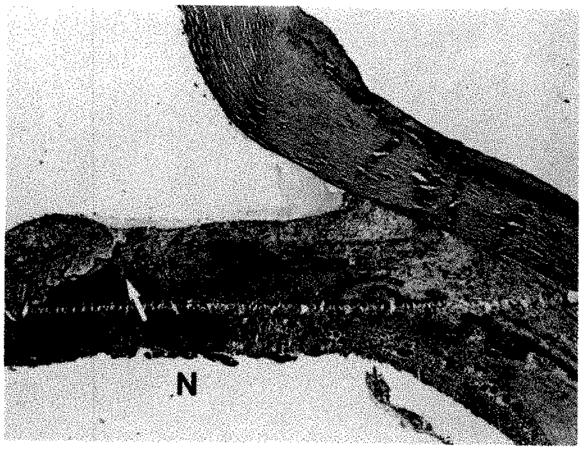

Fig. 2 (Margo and associates). Vertical section of the eye at the nasal border of the superior iridotomy shows severe inflammation of the iris. The torn end of the lens capsule (arrow) is drawn into the iris defect next to the rolled edge of the iridotomy. A thick mantle of suppurative and granulomatous inflammation surrounds the lens nucleus (N), which has been displaced inferiorly (PAS, × 23).

When we examined the patient eight weeks after the procedure the left pupil was filled with white flocculent material (Fig 1). A hypopyon and large keratic precipitates were present. The edge of the lens was not visible through either iridotomy. The right eye showed no signs of inflammation. A diagnosis of granulomatous endophthalmitis was made and enucleation advised. Relevant histologic findings included several large tears in the anterior lens capsule associated with suppurative and granulomatous inflammation surrounding exposed lens fibers (Fig. 2). The lens nucleus was dislocated inferiorly. Spillover from the acute inflammatory reaction involved the anterior chamber, uveal tract, peripheral retina, and anterior vitreous. The free edge of iris at the superior iridotomy was rolled posteriorly, which explained why clinically it resembled a surgical iridectomy.

Despite the potential for Nd:YAG iridotomy to damage the anterior lens capsule, inadvertent injury to the crystalline lens is exceptionally rare.[1-4] We suspect several factors may have contributed to capsular rupture in our patient. The most important of these was the large and relatively central location of the superior iridotomy. The presence of posterior synechiae also reduced the distance between the iris and anterior lens capsule, increasing the risk of capsular tear.

References

1. Drake, D. V.: Neodymium:YAG laser iridotomy. Surv. Ophthalmol. 32:171, 1987.
2. Berger, C. M., Lee, D. A., and Christensen, R. E.: Anterior lens capsule perforation and zonular rupture after Nd:YAG laser iridotomy. Am. J. Ophthalmol. 107:674, 1989.
3. Belch, D. B., Apple, D. J., Mendelsohn, A. D., Reidy, J. J., Chalkeley, T. H. F., and Wilensky, J. T.: Lens injury following iridotomy with a Q-switched neodymium laser. Arch. Ophthalmol. 104:123, 1986.
4. Montgomery, D. M. I., and Button, D. N.: Intralenticular haemorrhage complicating pulsed laser iridotomy. Br. J. Ophthalmol. 71:484, 1987.

Hypertropia After Implantation of a Molteno Drainage Device

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Molteno implants are frequently used in the treatment of difficult glaucoma. Strabismus is a rare complication of this procedure.[1] We treated a patient who developed progressive strabismus after implantation of a Molteno drainage device.

A 63-year-old man had a history of open-angle glaucoma since 1975. In 1989 he had a retinal detachment in his left eye, which was repaired surgically with a radial 5-mm superior sponge and an encircling 2.5-mm hard silicone band. His glaucoma was poorly controlled and in November 1990 he underwent implantation of a single plate Molteno drainage device in the superotemporal quadrant of his left eye. The implant was placed 8 mm from the corneoscleral limbus with the posterior portion of the plate resting superficial to the encircling element.

Preoperatively he had a well-controlled, intermittent, right hypertropia of 8 prism diopters, which was also noticed two weeks after the surgery. By the fourth postoperative week the right hypertropia had changed to a left hypertropia of 16 prism diopters. In the sixth postoperative week the left hypertropia had increased to 25 prism diopters; two weeks later it mea-

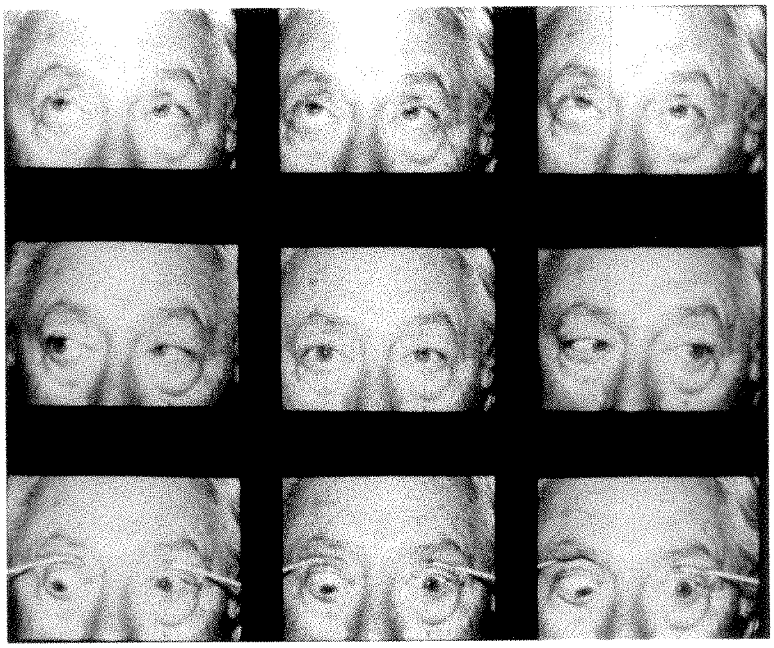

Figure (Muñoz and Parrish). Versions in the nine diagnostic positions of gaze show a left hypertropia of 45 prism diopters with severe limitation to depression of the left eye.

sured 45 prism diopters and has remained stable since then (Figure). The vertical deviation was accompanied by an exotropia of 14 prism diopters and 15 degrees of incyclotorsion. Ductions and versions showed severe limitation to depression of the left eye, both in abduction and adduction. Results of the Bielschowsky head tilt test were unequivocal. The forced duction test showed marked restriction on attempted depression of the left eye, and this was confirmed and quantitated with the differential intraocular pressure test.[2] The intraocular pressure of the left eye increased from 20 mm Hg in primary position to 45 mm Hg when measured while attempting depression.

External examination disclosed a thickened fibrotic diffuse bleb over the Molteno plate with no significant conjunctival scarring.

Previous reports of strabismus after Molteno implants described limitation of eye movement in the direction of the implant, thus producing vertical strabismus.[3,4] Possible explanations cited were the mechanical displacement by the large cyst and a Faden effect as the implant is encapsulated. Our patient's rapid progression of a restrictive left hypertropia after a Molteno implant in the superotemporal quadrant of his left eye suggests a different mechanism, a fat adherence syndrome. This syndrome results from accidental penetration of Tenon's capsule peripheral to 10 mm from the corneoscleral limbus, disrupting the fat pad and inducing inflammation and fibrosis of the extraconal septae that can now come in direct contact with the globe.[5] As the septae contract they pull the globe and produce a progressive restrictive strabismus. The fat pad might be disrupted while the surgeon is spreading the tissues with the scissors to place the Molteno implant equatorially, especially in re-operations. Careful dissection of the tissues and closure of Tenon's capsule when unintentionally opened may reduce the incidence of this complication.

References

1. Muñoz, M., Tomey, K., Traverso, C., Day, S. H., and Senft, S: Clinical experience with the Molteno implant in advanced infantile glaucoma. J. Pediatr. Ophthalmol. Strabismus 28:68, 1991.

2. Muñoz, M., and Capó, H.: Differential intraocular pressure in restrictive strabismus. Am. J. Ophthalmol. 112:352, 1991.

3. Wilson-Holt, N., Noureddin, B., Gregson, R., and Hitchings, R. A.: Hypertropia following inferiorly sited double plated Molteno tubes, abstract. Ophthalmology 97(suppl):147, 1990.

4. Christmann, L. M., and Wilson, E.: Motility disturbances after Molteno implants. J. Pediatr. Ophthalmol. Strabismus. In press.

5. Parks, M. M.: Causes of the adhesive syndrome. In Symposium on Strabismus. Transactions of the New Orleans Academy of Ophthalmology. St. Louis, C. V. Mosby, 1978, pp. 269–279.

Retinal Microvasculopathy and Reduced Cerebral Blood Flow in Patients With Acquired Immunodeficiency Syndrome

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Retinal microvasculopathy is a frequent finding in patients with acquired immunodeficiency syndrome or human immunodeficiency virus-related diseases. This retinopathy includes cotton-wool spots, retinal hemorrhages, and microvascular abnormalities.[1,2] Fluorescein angiography shows microaneurysms, telangiectasis, focal areas of nonperfusion with capillary dropout, and focal leakage. Cotton-wool spots are typically associated with focal leakage and focal nonperfusion.[3] These lesions are similar to those seen in diabetes mellitus or systemic lupus erythematosus and other non-HIV-related diseases.

Cerebral microvascular involvement is well known for systemic lupus erythematosus and has been described for diabetes mellitus.[4] No association could be established between ocular HIV-related microvasculopathy and any symptoms studied.[2] An association between the presence of cotton-wool spots and higher serum levels of fibrin has been reported.[5] Functional cerebral damage is a frequent finding in patients with full-blown AIDS and is sometimes called AIDS-dementia.

To determine a possible association of ocular HIV-related microvasculopathy with cerebral blood flow we performed ophthalmologic investigation and technitium-99m-hexamethyl-propyleneamine oxime single photon emission computed tomography of the brain in 25 patients with AIDS or symptomatic HIV infection. All patients gave informed consent. No patient had diabetes mellitus or any other disease known to cause ocular microvasculopathy. All patients were homosexual or bisexual and had no history of drug abuse.

To measure the degree of ocular HIV-related microvasculopathy we counted the number of cotton-wool spots by indirect ophthalmoscopy in both eyes of each patient (Figure). The number of cotton-wool spots in both eyes was added to one score. Fundus examination was performed after the pupils were dilated by an ophthalmologist with a 15-diopter lens. Technitium-99m-hexamethyl-propyleneamine oxime single photon emission computed tomography is a valid method for imaging cerebral blood flow and has gained special interest in the investigation of cerebrovascular disease and dementia. After intravenous injection of 370 to 550 milibecquerel of technetium-99m-hexamethyl-propyleneamineoxime, single photon emission computed tomography was

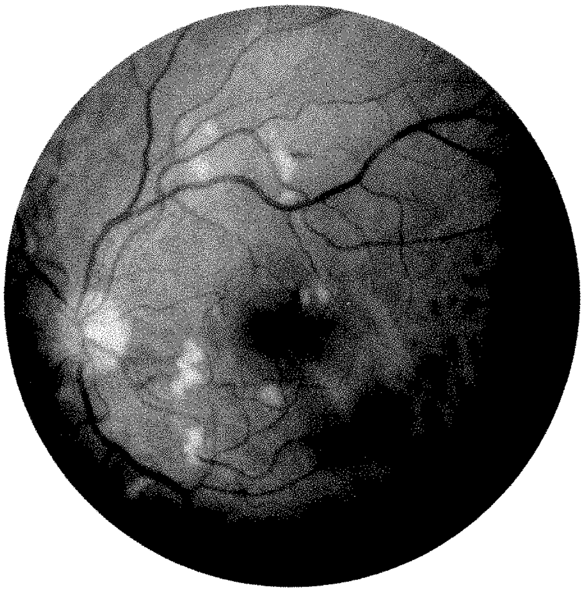

Figure (Geier and associates). Full-blown ocular microvasculopathy with 18 cotton-wool spots in a patient with reduced cerebral blood flow (hexamethyl-propyleneamine oxime single photon emission computed tomography value II).

performed with a rotating double head gamma camera connected to a MicroDelta/Vax 11/730 computer system. Data were collected from 60 projections in a 64 × 64-matrix. Images were reconstructed by filtered backprojection. Transverse, sagittal, and coronal slices were proccessed. Single photon emission computed tomography findings were semiquantitatively evaluated by using the region of interest technique. Six right over left gray matter ratios of corresponding regions were calculated in selected transverse slices. A difference in ratios of more than 2 standard deviations of the normal population was considered pathologic. Results were classified into three groups: 0 = normal findings; I = one or two areas of decreased activity in two or more consecutive slices; and II = three or more areas of decreased activity. All patients were anti-HIV IgG ELISA-positive confirmed by Western blot technique. Patients were classified according to the Walter Reed classification (WR) and absolute CD4+ lymphocyte count was determined by FACScan. Thirteen patients had AIDS (WR 6). Five patients were classified WR 5; two, WR 4; two, WR 3; and three patients were classified WR 2. Statistical analysis was performed on an IBM-PS/2 with the SAS software (SAS Institute, Cary, North Carolina).

To determine a possible association between the number of cotton-wool spots and hexamethyl-propyleneamine oxime single photon emission computed tomography we used the Spearman correlation coefficient. Six patients had hexamethyl-propyleneamine oxime single photon emission computed tomography value 0, nine had value I, and ten had value II. No patient with hexamethyl-propyleneamine oxime single photon emission computed tomography value 0 had any cotton-wool spots although four of the six patients were classified as WR 5 or 6. The Spearman correlation coefficient between the number of cotton-wool spots and hexamethyl-propyleneamine oxime-single photon emission computed tomography was .71 ($P < .0001$).

This finding suggests a statistically significant and clinically relevant association between the number of cotton-wool spots and cerebral blood flow. Because the number of cotton-wool spots is related to the degree of retinal microvasculopathy, this result also suggests a significant association between HIV-related microvasculopathy and cerebral blood flow in AIDS patients and HIV-positive patients. Spearman correlations between the number of cotton-wool spots and Walter Reed classification ($r = .64$; $P = .0006$) as well as between the number of cotton-wool spots and CD4+ count ($r = -.57$; $P = .004$) were lower than the correlation between hexamethyl-propyleneamine oxime single photon emission computed tomography and the number of cotton-wool spots. Spearman correlations between hexamethyl-propyleneamine oxime single photon emission computed tomography and Walter Reed classification ($r = .28$; $P = .21$) as well as between hexamethyl-propyleneamine oxime single photon emission computed tomography and CD4+ count ($r = -.32$; $P = .13$) were not significant. This pattern of associations is another hint concerning the importance of microvascular disease in HIV-infected patients. The pathogenic mechanisms underlying ocular HIV-related microvasculopathy are not known and may be multifactorial. There is a hypothesis that HIV-infection of vascular endothelium may lead to microvascular changes. The possibility of systemic hemorheologic factors should also be discussed. Our results suggest the possibility that systemic and local microvascular changes in AIDS patients contribute not only to the development of cotton-wool spots but also to the development of decreased cerebral blood flow. Further studies are needed to measure cerebral and ocular blood flow and its association with functional cerebral and ocular damage in AIDS patients.

References

1. Pepose, J. S., Holland, G. N., Nestor, N. S., Cochran, A. J., and Foos, R. Y.: Acquired immunodeficiency syndrome. Pathogenic mechanisms of ocular disease. Ophthalmology 92:472, 1985.
2. Freeman, W. R., Chan, A., Henderly, D. E., Levin, A. M., Ludbrul, J. K., Uria, P. T., Arthur, J., Rashid, S., Cohan, J. L., Neuberg, D., and Leun, R. J.: Prevalence and significance of acquired immunodeficiency syndrome-related retinal microvasculopathy. Am. J. Ophthalmol. 107:229, 1989.
3. Newsome, D. A., Green, R. W., Miller, E. D., Kiessling, L. A., Morgan, B., Jabs, D. A., and Polk, B. F.: Microvascular aspects of acquired immunodeficiency syndrome retinopathy. Am. J. Ophthalmol. 98:590, 1984.
4. Frank, R. N.: On the pathogenesis of diabetic retinopathy. Ophthalmology 98:586, 1991.
5. Engstrom, R. E., Holland, G. N., Hardy, W. D., and Meiselman, H. J.: Hemorheologic abnormalities in patients with acquired immunodeficiency virus infection and ophthalmic microvasculopathy. Am. J. Ophthalmol. 109:153, 1990.

Simultaneous Herpes Simplex Types 1 and 2 Keratitis in Acquired Immunodeficiency Syndrome

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Herpes simplex virus types 1 and 2 are well established causative agents for keratitis. Confirmation of infection can be obtained by viral culture and subsequent immunofluorescent antibody staining with type-specific monoclonal antibodies. We have recently seen a case of dendritic keratitis that proved to contain active herpes simplex virus type 1 and herpes simplex virus type 2. The patient showed no initial distinguishing factors to indicate multiple infectious serotypes.

A 38-year-old man known to have acquired immunodeficiency syndrome (AIDS) was seen because of ocular discomfort in his left eye. He reported pain, photophobia, and decreased vision. Examination disclosed a visual acuity of 20/60. On external examination, facial lesions of Kaposi's sarcoma and molluscum contagiosum were seen in the left upper and lower eyelids (Fig. 1). Preauricular lymphadenopathy was absent. Slit-lamp examination of the left eye disclosed a large central dendrite with typical end bulbs suggestive of herpes simplex virus keratitis (Fig. 2). No anterior chamber or conjunctival reaction was observed. The fundus in the left eye was normal.

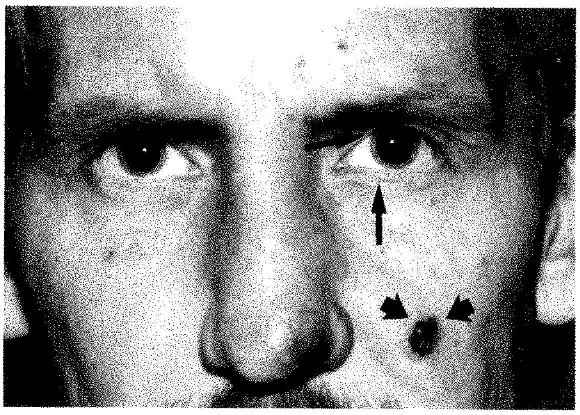

Fig. 1 (Rosenwasser and Greene). Kaposi's sarcoma (thick arrows) and molluscum contagiosum lesion (thin arrows) in a patient with AIDS.

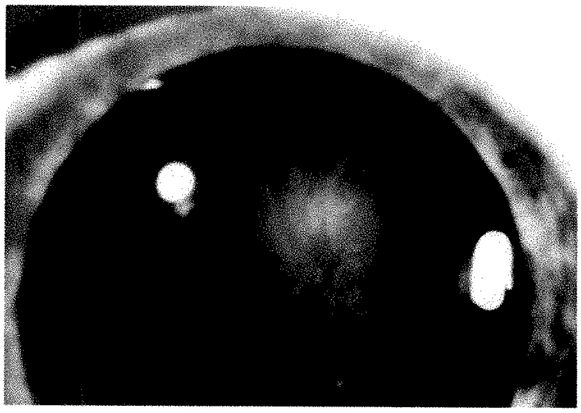

Fig. 2 (Rosenwasser and Greene). Epithelial dendrite resulting from simultaneous infection with herpes simplex virus types 1 and 2.

Viral culture of the dendrite was obtained with a Dacron swab and placed in viral transport media. Treatment was initiated with trifluridine 1.0% every two hours for a total of nine daily doses. Treatment was continued at that dose for one week and tapered to four times a day over the following week after resolution of the surface dendrite. A third week of treatment with tapering dosage was continued until topically administered trifluridine was stopped. Visual acuity returned to 20/25 and the patient was symptom-free. A minimal punctate epithelial keratitis was present.

Culture of the specimen obtained was performed according to our standard procedure of inoculating rabbit kidney, MRC-5, and A-549 cells. Cytopathic effect characteristic of herpes simplex virus was noted the following day in the rabbit kidney cells and was subsequently observed in the MRC-5 and A-549 cells. Culture confirmation using fluorescein-labeled monoclonal antibodies specific for herpes simplex virus type 1 or type 2 indicated the presence of both serotypes of herpes simplex virus. Repeat staining with additional monoclonal antibodies from two different manufacturers also indicated the presence of both serotypes. The two viruses were separated by passing the original specimen through two cycles of plaque purification. Separation was possible because herpes simplex virus type 1 tends to produce smaller plaques than herpes simplex virus type 2. Pure cultures of herpes simplex virus type 1 and herpes simplex virus type 2 were obtained and confirmed by using the monoclonal antibody reagents.

Herpes keratitis has been reported to occur predominantly from herpes simplex virus type 1 infection. The herpes simplex virus type 2 serotype has conventionally been associated with the sexually transmitted form of the disease but has also been reported to be an ocular pathogen that causes keratitis indistinguishable from herpes simplex virus type 1. Although previous reports have dealt with the appearance of herpetic keratitis in individuals with AIDS,[1] we believe this is a unique case of a simultaneous infection with both herpes simplex virus types 1 and 2 serotypes.

The patient had no history of previous keratitis or ocular abnormalities. The episode did not appear to be remarkably different from those seen in single serotype infections, though inflammation (conjunctival follicles and preauricular lymphadenopathy) was conspicuously absent. Treatment allowed resolution with return of visual acuity to 20/25 within three weeks. Prolongation of the course was not obvious.

Reference

1. Young, T., Robin, J. B., Holland, G. N., Hendricks, R. L., Paschal, J. F., Engstrom, R. E., and Sugar, J.: Herpes simplex keratitis in patients with acquired immune deficiency syndrome. Ophthalmology 96:1476, 1989.

Delayed Bilateral Involvement in the Acute Retinal Necrosis Syndrome

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In July 1965, an 18-year-old woman was seen by her ophthalmologist because of decreased vision, redness, and pain in her left eye. Examination disclosed a severe vitreitis that obscured the fundus. Over the next two months, the patient's visual acuity in the left eye worsened to no light perception. The right eye remained normal. The patient denied any systemic symptoms or signs associated with this progressive visual loss. During these two months, the treating ophthalmologist examined the patient many times and was unable to reach a diagnosis.

In February 1991, this patient, now 44 years old, was referred to our institution. She had a five-day history of increasing redness, pain, photophobia, and decreasing vision in her previously unaffected right eye. Her referring ophthalmologist had diagnosed iritis, and four days previously had initiated corticosteroid and cycloplegic therapy. Her visual acuity was 20/200 and her intraocular pressure was 24 mm Hg. The pupil was dilated. The anterior segment had a moderate iridocyclitis. Ophthalmoscopy indicated marked vitreitis, obscuring fine details of the disk and macula. A confluent peripheral vaso-occlusive necrotizing retinitis extended around the entire retinal periphery and encroached on the vascular arcades. The retinal vessels were attenuated, and scattered areas of intraretinal hemorrhage were present. Examination of the left eye disclosed visual acuity of no light perception, a quiet anterior segment, an intraocular pressure of 10 mm Hg, and a total retinal detachment with proliferative vitreoretinopathy.

Acute retinal necrosis was diagnosed. The patient was admitted and started on a ten-day course of intravenously administered acyclovir. Results of laboratory studies were noncontributory. Human immunodeficiency virus testing was negative. Three days after initiating acyclovir therapy, systemic corticosteroids were begun. Prophylactic laser therapy could not be performed because of the vitreous debris. The retinitis and vitreitis responded to the acyclovir. The patient's course was complicated five weeks later by a combined rhegmatogenous and tractional retinal detachment, which was repaired by pars plana vitrectomy with endolaser and silicone oil. Visual acuity remained hand motions.

Acute retinal necrosis occurs bilaterally in approximately one third of the patients, with the fellow eye usually affected within two months after the first eye[1]; however, time intervals between eyes of up to 19 years have been reported.[2] Our case documents a 26-year interval between affected eyes.

This case also demonstrates the devastating effects of acute retinal necrosis. Well over 50% of patients affected by acute retinal necrosis become legally blind.[3] Although more recent reports show a better prognosis as the result of modern vitrectomy techniques, retinal tears, vitreous fibrosis, and traction lead to rhegmatogenous retinal detachment and proliferative vitreoretinopathy in up to 75% of cases.[4] These retinal detachments typically occur weeks after onset and are usually responsible for the poor visual outcome. Although bilaterality is common without treatment, it has been demonstrated recently that treatment of the first eye with acyclovir reduces the likelihood that acute retinal necrosis will develop in the fellow eye.[5]

References

1. Charles, H.: Acute retinal necrosis. In Tasman, W., and Jaeger, E. A. (eds.): Duane's Clinical Ophthalmology. Philadelphia, J. B. Lippincott, 1990, vol. 4., chap. 47, p. 5.
2. Rabinovitch, T., Nozik, R. A., and Varenhorst, M. P.: Bilateral acute retinal necrosis syndrome. Am. J. Ophthalmol. 108:735, 1989.
3. Fisher, J. P., Lewis, M. L., Blumenkranz, M. S., Culbertson, W. W., Flynn, H. W., Clarkson, J. G., Gass, J. D., and Norton, E. W.: The acute retinal necrosis syndrome. I. Clinical manifestations. Ophthalmology 89:1317, 1982.
4. Blumenkranz, M. S., Clarkson, J. G., Culbertson, W. W., Flynn, H. W., Lewis, M. L., and Young, G. M.: Visual results and complications after retinal reattachment in the acute retinal necrosis syndrome. Retina 9:170, 1989.
5. Palay, D. A., Sternberg, P., Jr., Davis, J., Lewis, H., Holland, G. P., Mieler, W. F., Jabs, D. A., and Drews, C.: Decrease in the risk of bilateral acute retinal necrosis by acyclovir therapy. Am. J. Ophthalmol. 112:250, 1991.

Locally Administered Hyperoxic Therapy for Aphakic Cystoid Macular Edema

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We evaluated the effect of locally delivered oxygen on a group of patients with chronic aphakic cystoid macular edema to determine if it would produce a similar improvement in vision to that reported with hyperbaric oxygenation.[1] To facilitate the delivery of oxygen to the eye we created a localized hyperoxic chamber over the eye by modifying a pair of swimmer's goggles. A length of silicone tubing was secured inside of one of the goggle eyepieces and used to direct humidified 100% oxygen into the goggle chamber (Figure). Before initiating the study we measured the pressure inside of the goggle chamber at different flow rates of oxygen. The pressure inside the goggle chamber increased from a baseline of 763 ± 2 mm Hg with the oxygen off to 768 ± 3 mm Hg when the flow rate was increased to 0.5 l/minute. Increasing the flow rate beyond this level only produced a modest increase in pressure because of leakage of oxygen around the foam rubber seal of the goggle.

Three patients with chronic aphakic cystoid macular edema at the Second Affiliated Hospital in Wenzhou, The People's Republic of China, were treated with locally administered hyperoxic therapy. All three patients had previously undergone intracapsular cataract standard extraction with forceps, complicated by vitreous loss. Their cystoid macular edema had not been treated, as was customary at that time. After giving informed consent, each patient completed a screening questionnaire, an eye examination including refraction was per-

Figure (Benner and Miao). The modified swimmer's goggles with the silicone tubing inserted into one of the eyepieces to create a hyperoxic chamber over the eye.

formed, and fluorescein angiography was performed. Angiography disclosed that all three patients had classic petaloid cystoid macular edema. Visual acuity had been reduced for 22 months, 19 months, and six years, respectively. Each of the patients then completed a three-week course of hyperoxic goggle therapy, which consisted of 0.5 l/minute of humidified 100% oxygen administered to the affected eye for six hours per day for six days of each week.

The three patients treated in this pilot study all had longstanding aphakic cystoid macular edema with obvious vitreous humor to the wound. Despite the severity of the cystoid macular edema all three patients had marked improvement in their visual function after five to seven days of locally administered hyperoxic therapy.

Visual acuity in the first patient improved from 20/80 to 20/40 on the fifth day of treatment and ultimately improved to 20/30 at the six- and ten-month follow-up visits. Visual acuity in the second patient improved from 20/60 to 20/40 on the fifth day of treatment, and the patient had additional improvement to 20/30 at the six- and ten-month visits. The third patient improved in visual acuity from 20/80 to 20/60 on the seventh day of treatment. This patient did not return for follow-up. The two patients who returned for follow-up had normal foveal appearance for the ten-month interval of this study. There were no biomicroscopic or ophthalmoscopic changes associated with the locally administered oxygen. The only patient complaint was boredom from sitting in an isolated treatment room for six hours each day.

Pfoff and Thom[1] reported a similar improvement in vision in five patients with chronic pseudophakic cystoid macular edema treated with intermittent hyperbaric oxygenation at 2.2 atmospheres for three weeks. They suggested that this improvement was caused by a hyperoxic vasoconstriction of the parafoveal capillaries, which allowed for the reformation of junctional complexes between the endothelial cells. Perhaps the parafoveal inner retina is uniquely sensitive to reductions in its partial pressure of oxygen (PO_2) because of its high density of ganglion cells (five to seven layers) and other highly metabolic neural elements. Reductions in the preretinal PO_2 from postoperative inflammation or other factors might cause the autoregulated parafoveal vasculature to vasodilate focally in order to maintain a minimal oxygen tension. Over time this chronic vasodilation might lead to a breakdown in the integrity of the endothelial tight junctions, producing leakage and the characteristic intraretinal edema seen in cystoid macular edema. Increasing the PO_2 of this tissue to supranormal levels would cause these parafoveal vessels to vasoconstrict, allowing unopposed clearance of the intraretinal edema and the integrity of the blood-retinal barrier eventually to be restored. The local delivery of 100% oxygen with goggles doubled the PO_2 of the aqueous humor of the rabbit within 30 minutes[2] and might also produce a similar increase of the inner retinal PO_2 in an aphakic eye.[3]

References

1. Pfoff, D. S., and Thom, S. R.: Preliminary report on the effect of hyperbaric oxygen on cystoid macular edema. J. Cataract Refract. Surg. 13:136, 1987.
2. Jampol, L. M., Orlin, C., Cohen, S. B., Zanetti, C., Lehman, E., and Goldberg, M. F.: Hyperbaric and transcorneal delivery of oxygen to the rabbit and monkey anterior segment. Arch. Ophthalmol. 106:825, 1988.
3. Stefansson, E., Landers, M. B., and Wolbarst, M. L.: Increased retinal oxygen supply following pan-retinal photocoagulation and vitrectomy and lensectomy. Trans. Am. Ophthalmol. Soc. 79:307, 1981.

Macular Edema After Carotid Endarterectomy in Ocular Ischemic Syndrome

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We recently treated a patient with anterior uveitis who successfully underwent an endarterectomy for a 90% to 95% internal carotid artery obstruction. He subsequently developed diabetic retinopathy with macular edema, which had not been present preoperatively.

A 71-year-old man had a one-week history of a painful, red right eye, which had not responded to topical treatment with corticosteroids,

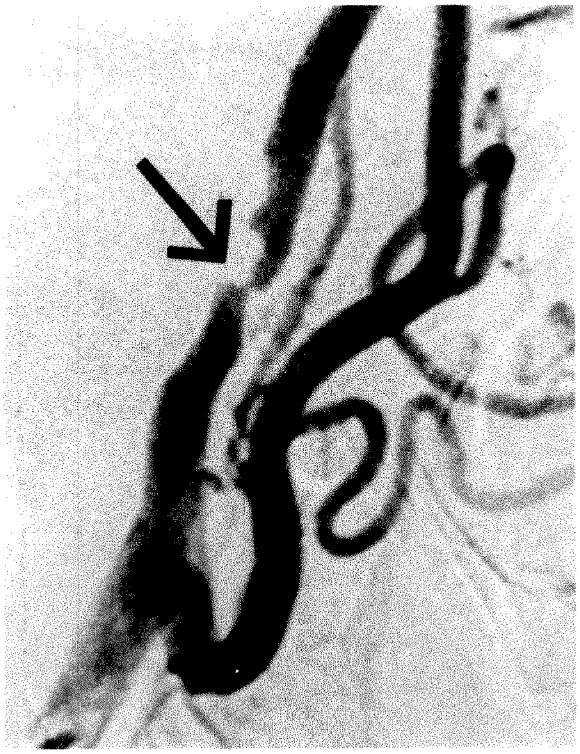

Fig. 1 (Bierly and Dunn). Digital subtraction angiogram of the right internal carotid artery demonstrating a 90% to 95% obstruction (arrow).

antibiotics, and cycloplegics. The patient had non-insulin-dependent diabetes mellitus, atherosclerotic heart disease, and claudication. His visual acuity was R.E.: counting fingers at 10 feet and L.E.: 20/30. In the right eye, the conjunctiva had a diffuse moderate injection. There was a striate keratopathy without keratic precipitates. The anterior chamber showed moderate cell and severe flare with a fibrin clot. There were no iris nodules, and the angle was open without neovascularization. The anterior segment was unremarkable in the left eye. Tension by applanation tonometry was 12 mm Hg in each eye. The vitreous was clear in both eyes. The retinas showed arteriolar narrowing in both eyes, and mild background diabetic retinopathy in the left eye but no retinopathy in the right eye. Diagnostic tests included a normal sedimentation rate, and a nonreactive fluorescent treponemal antibody test. A fluorescein angiogram showed a marked delay in the arm-to-choroid transit time (50 seconds), and a prolonged arteriovenous transit time of approximately 20 seconds. There was no evidence of neovascularization or staining of the vessels.

We made a presumptive diagnosis of ocular ischemic syndrome masquerading as an anterior uveitis. The uveitis slowly responded to topical treatment with corticosteroids and cycloplegics, with significant clearing of the anterior chamber reaction and improvement of the visual acuity to 20/60. Carotid artery noninvasive testing showed only a 50% obstruction. However, a digital subtraction angiogram showed a 90% to 95% obstruction of the right internal carotid artery 2 cm distal to the bifurcation of the carotid artery (Fig. 1). Additionally, the ophthalmic artery appeared to fill in a retrograde fashion through collaterals from the external carotid artery. Subsequently, the patient underwent a successful endarterectomy. He immediately had a subjective improvement in visual acuity to 20/30. However, six weeks postoperatively he complained of a decrease in

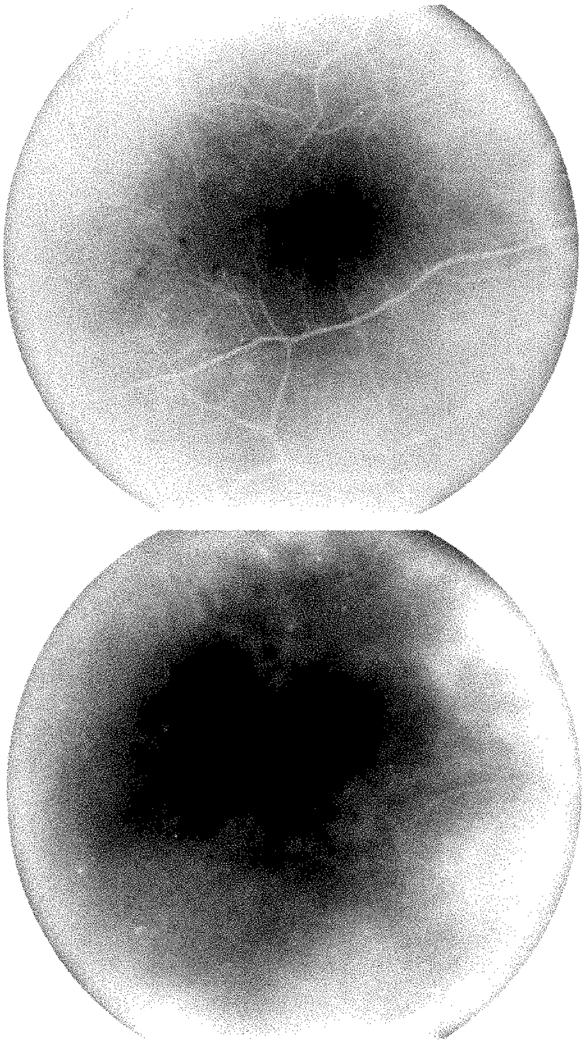

Fig. 2 (Bierly and Dunn). Fluorescein angiogram after carotid endarterectomy. Early venous phase (top) shows small microaneurysms that leak in the late venous phase (bottom), demonstrating cystoid macular edema

vision of the affected right eye, and at that time his best-corrected visual acuity was R.E.: 20/40 −2 and L.E.: 20/25. He had developed background diabetic retinopathy with microaneurysms and macular edema in the right eye. A repeat fluorescein angiogram showed greatly improved circulation to the right eye (decreased arm-to-choroid transit time and decreased arteriovenous transit time). Cystoid macular edema was also present, which had not been present preoperatively (Fig. 2).

Ocular ischemic syndrome often manifests with neovascularization of the posterior or anterior segment in the setting of severe carotid vascular disease. Venous-stasis retinopathy, iritis, and central retinal artery occlusion are other manifestations. Iritis in the absence of rubeosis, as was seen in this patient, has been reported rarely.[1,2] The development of macular edema after endarterectomy should be added to other complications of this procedure.[3] It is unclear if a hemodynamically significant carotid artery stenosis protects against the development of proliferative diabetic retinopathy.[4] This case raises the question of whether there may be a protective effect with regard to background diabetic retinopathy and macular edema.

References

1. Brown, G. C., and Magargal, L. E.: The ocular ischemic syndrome. Int. Ophthalmol. 11:239, 1988.
2. Knox, D. L.: Ischemic ocular inflammation. Am. J. Ophthalmol. 60:995, 1965.
3. Melamed, S., Irvine, J., and Lee, D. A.: Increased intraocular pressure following endarterectomy. Ann. Ophthalmol. 19:304, 1987.
4. Duker, J. S., Brown, G. C., Bosley, T. M., Colt, C. A., and Reber, R.: Asymmetric proliferative diabetic retinopathy and carotid artery disease. Ophthalmology 97:869, 1990.

Episodic Bilateral Corneal Edema Caused by Hair Groom Gel

Denise Satterfield, M.D.,
and Mark J. Mannis, M.D.

Department of Ophthalmology, University of California, Davis.

Inquiries to Mark J. Mannis, M.D., Department of Ophthalmology, University of California, Davis, 1603 Alhambra Blvd., Sacramento, CA 95816.

Bilateral corneal edema is associated with several systemic and ocular disorders as well as ocular infection, trauma (mechanical, surgical or chemical), inflammation, and increased intraocular pressure. We treated a patient with episodic bilateral corneal edema with complete and spontaneous resolution between episodes.

A 57-year-old man was referred our institution because of a four-year history of intermittent bilateral corneal edema of unknown cause. He complained of marked "smoky" visual loss with slight discomfort in both eyes. These episodes occurred only in hot weather with exertion and spontaneously resolved within 24 to 36 hours. During symptomatic periods, findings included a documented decrease in vision, moderate conjunctival injection with a mild papillary response, and diffuse stromal and epithelial corneal edema with punctate epithelial staining (Figure). Anterior chambers and irides were unremarkable. Intraocular pressure in each eye was 18 mm Hg. Between episodes results of the ocular examination were normal.

He was treated with sodium chloride 5% ophthalmic solution symptomatically during episodes of edema. He had no known allergies. Significant medical problems included moderate obesity, pulmonary fibrosis, coronary artery disease, insulin-dependent diabetes mellitus, acephalgic migraines, and arthritis. Systemic

Figure (Satterfield and Mannis). Appearance of both corneas during an acute episode of diffuse stromal and epithelial edema, punctate epithelial keratopathy, and hyperemic conjunctiva. The epithelial edema blurs iris detail.

medications included insulin, isosorbide, and naproxen.

On further questioning, the patient stated that perspiration would run into his eyes when he exerted himself in the heat. The one time that he wore a sweat band, he did not recall having problems with his eyes. He used Mennen Protein 29 Clear Gel Hair Groom regularly. We recommended that he stop the use of this product and continue with his activities. The episodes of corneal edema stopped abruptly even with exertion and significant perspiration in hot weather. This patient had experienced episodic bilateral corneal edema for years because of perspiration running into his eyes carrying with it substances from the hair groom product he was using.

Systemic causes of bilateral corneal edema include polyarteritis nodosa, Reiter's syndrome, Werner's syndrome, cerebrohepatorenal syndrome, phakomatoses, Refsum's disease, serum sickness, and relapsing fever. Primary ocular disorders that cause bilateral corneal edema include the posterior corneal dystrophies (congenital hereditary endothelial dystrophy, Fuchs' dystrophy, and posterior polymorphous dystrophy) and bilateral iridocorneal-endothelial syndrome. Secondary ocular conditions that can lead to bilateral corneal edema, if affecting both eyes, include inflammation (Cogan-Reese syndrome, uveitis), infections (herpes simplex virus, herpes zoster virus), and acute or chronic glaucoma. Trauma in many forms can lead to corneal edema. Surgical damage, chemical exposure, penetrating and nonpenetrating injuries, contact lens wear, and radiation damage are some examples.

Numerous topical agents can cause corneal edema, including a variety of antibiotics and anesthetics. Systemic medication with some antipsychotic, antimalarial, and antihelmintic agents can lead to corneal edema. Silicone, intraocular lenses, lubricants, retinal tacks, and volume expanders may cause corneal edema when placed in the eye.[1]

This patient's history was inconsistent with a primary ocular disorder or a systemic disease, but suggested a recurring insult to both eyes over a period of several years. Mennen Protein 29 Clear Gel Hair Groom contains water, mineral oil, oleth-10, propylene glycol, oleth-3 phosphate, lanolin alcohol, oleth-20, triethanolamine, hydrolyzed animal protein, methylparaben, quaternium-15, fragrance, and FD&C green No. 3. Two of the ingredients, triethanolamine and quaternium-15, are anionic detergent compounds that can cause ocular irritation. Specifically, they may cause immediate discomfort, edema of the corneal epithelium, and punctate staining with fluorescein as well as conjunctival hyperemia. These clear within a day or two and without residual corneal opacity (Poisindex Substance Identification, product reference 265S776. Micromedex, Inc., Denver, Colorado).

Reference

1. Fraunfelder, F. T.: Drug-Induced Ocular Side Effects and Drug Interactions, ed. 2, Philadelphia, Lea and Febiger, 1989, pp. 506–507.

Conjunctival Granulomas in Rosace

Darren Lee Albert, M.D.,
Seymour Brownstein, M.D.,
and W. Bruce Jackson, M.D.

Departments of Ophthalmology (D.L.A., S.B., W.B.J.) and Pathology (D.L.A., S.B.), McGill University, Royal Victoria Hospital.

Inquiries to Seymour Brownstein, M.D., Dept. of Ophthalmology, Royal Victoria Hospital, 687 Pine Ave. W., Ste. E4.61, Montreal, Quebec, Canada H3A 1A1.

Rosacea is a chronic skin disease, usually limited to the face and neck, which is characterized by erythema, telangiectasia, papules, pustules, and hypertrophic sebaceous glands, all in varying degrees. It affects blacks as well as whites and occurs most commonly in adults.

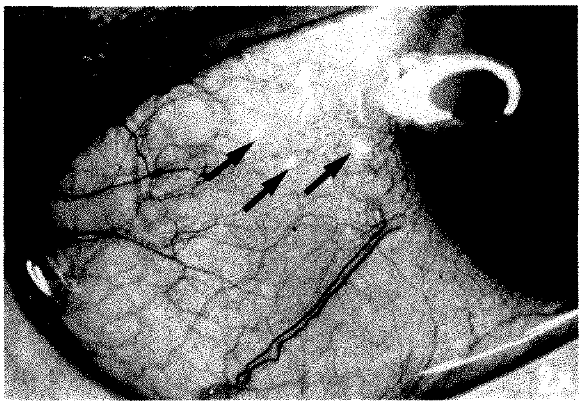

Fig. 1 (Albert, Brownstein, and Jackson). Right eye shows bulbar conjunctival small nodules at and adjacent to the highlights (arrows). The conjunctival and episcleral vessels are dilated.

Ocular involvement is seen in 3% to 58% of patients with rosacea and commonly takes the form of blepharitis, telangiectasia of the eyelid margin, hyperemic conjunctivitis, and keratitis.[1] Chalazia, styes, meibomianitis, superficial punctate keratopathy, and granulomas of the eyelid skin have also been described.[1,2]

A 69-year-old white woman was seen in February 1982 because of a two-month history of bilateral, watery, itchy, red eyes and mild morning crusting, associated with redness of her eyelids and a facial rash. She had been treated with chloramphenicol eyedrops, saline compresses, and eyelid scrubs with no improvement. Uncorrected visual acuity was 20/30 in both eyes. An erythematous facial rash with scattered papules and telangiectasia, was noted. Slit-lamp examination disclosed bilateral palpebral papillary reactions and numerous small bulbar conjunctival nodules similar in appearance to follicles and, in the right eye, fascicular keratitis, dilated conjunctival and episcleral vessels, and mild blepharitis (Fig. 1). The patient had had intermittent conjunctivitis for four years. Her medical history included Raynaud's phenomenon, esophageal spasm, mild hypertension, posttraumatic cervical arthritis, inflammatory polyarthritis, allergic rhinitis, and allergic asthma. She was taking ibuprofen for headaches.

The patient was treated with erythromycin, 250 mg orally four times a day. Both her facial rash and conjunctival nodules improved after three weeks. She continued taking erythromycin, 250 mg orally twice daily, for two more years at which time she showed no further evidence of facial, eyelid, conjunctival, or corneal abnormalities. In April 1991, she returned with recurrence of both her facial rash and conjunctival nodules, which were asymptomatic.

Histopathologic examination of two conjunctival biopsy specimens from February 1982 showed several discrete, epithelioid cell granulomas containing occasional multinucleated giant cells and surrounded by lymphocytes and plasma cells (Fig. 2). There was no evidence of foreign material under polarized light, and special stains for microorganisms were negative. The serum angiotensin-converting enzyme was mildly increased to 565 nmol/l (normal, 140 to 530 nmol/l) and skin tests were negative for purified protein derivative, *Candida* and *Trichophyton* species. Serologic testing for *Treponema pallidum*, the hemogram, serum calcium, serum immunoglobulins, C3 complement, rheumatoid factor, and chest x-ray were all within normal limits.

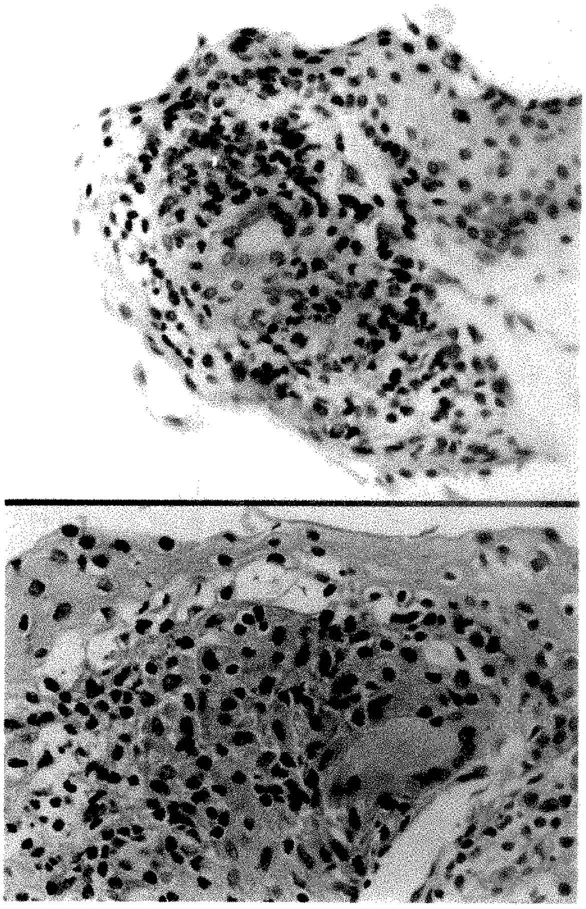

Fig. 2 (Albert, Brownstein, and Jackson). Conjunctival biopsy specimens show discrete, epithelioid cell granulomas with multinucleated giant cells (hematoxylin-eosin, top, × 250; bottom, × 400).

Conjunctival granulomas rarely have been reported in patients with rosacea.[3-5] Supporting this association in our patient were the simultaneous response of the facial and ocular findings to antibiotic therapy, confinement of the granulomas to the bulbar conjunctiva, and no definitive evidence of other systemic diseases despite a mildly increased serum angiotensin-converting enzyme and anergy. We thus recommend that rosacea be included in the differential diagnosis of conjunctival granulomas.

References

1. Browning, D. J., and Proia, A. D.: Ocular rosacea. Surv. Ophthalmol. 31:145, 1986.

2. Patrinely, J. R., Font, R. L., and Anderson, R. L.: Granulomatous acne rosacea of the eyelids. Arch. Ophthalmol. 108:561, 1990.

3. von Szily, A.: Zur klinik und pathologischen anatomie der rosazea des auges. Klin. Monatsbl. Augenheilkd. 82:577, 1929.

4. Crick, R. P.: Diagnostic conjunctival biopsy in sarcoidosis. Trans. Ophthalmol. Soc. U.K. 12:403, 1968.

5. Hoang-Xuan, T., Rodriguez, A., Zaltas, M. M., Rice, B. A., and Foster, C. S.: Ocular rosacea. A histologic and immunopathologic study. Ophthalmology 97:1468, 1990.

Forceps for Lens Nucleus Extraction

Lawrence S. Evans, M.D.

Department of Ophthalmology, Stritch School of Medicine, Loyola University of Chicago.

Inquiries to Lawrence S. Evans, M.D., Department of Ophthalmology, Stritch School of Medicine, Loyola University of Chicago, 2160 S. First Ave., Maywood, IL 60153.

In extracapsular cataract surgery, one frequently encounters difficulty attempting to deliver the lens nucleus through a small pupil. I have designed forceps with an iris retractor on the proximal blade, which have proved useful in cases in which the iris did not dilate well before surgery and in which the iris constricted intraoperatively before delivery of the nucleus. The instrument has enabled me to avoid performing sphincterotomies and sector iridectomies on irides immobilized by conditions such as chronic miotic usage, atrophy from angle-closure glaucoma attacks, and iritis.

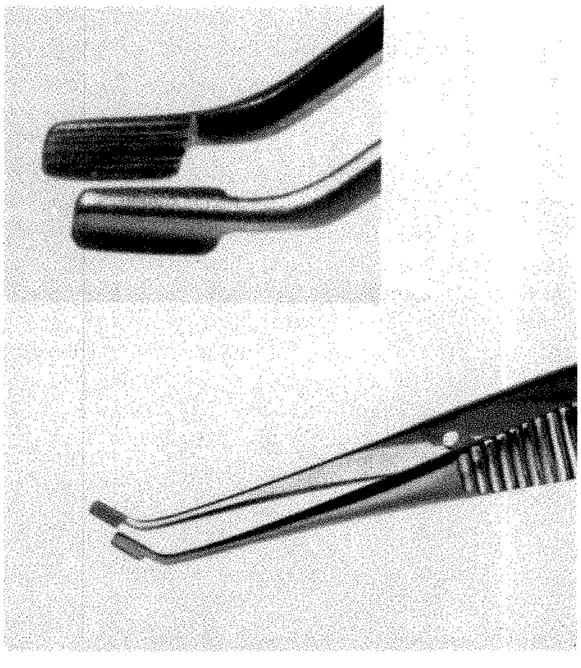

Fig. 1 (Evans). Lens forceps with iris retractor blade. The blade is concave to hold and retract the iris.

The handle and angulation of the blades of the instrument are similar to those of Arruga capsule forceps (Fig. 1). The proximal blade is concave, facing the surgeon, to retract the iris and to allow retraction in a broad arc. The distal blade is used to remove the dislocated nucleus. The insides of both blades are scored with horizontal ridges to improve grip. There are no teeth or sharp corners on the instrument.

The purpose of the instrument is to facilitate dislocation of the superior pole of the nucleus over the iris by retracting the iris and to utilize the same instrument to remove the nucleus from the eye. Viscoelastic material injected into the anterior chamber before performing the capsulotomy may help to keep the pupil enlarged and protect the corneal endothelium during the nucleus expression. The forceps are held in the right hand with the blades closed and the handle tilted back toward the surgeon so that the blades are parallel to the plane of the iris for insertion into the anterior chamber. The closed blades are introduced into the pupil to capture the iris, which is then retracted toward the surgeon. With a lens loop in the left hand, gentle pressure is then placed at the 6 o'clock position approximately 2 mm below the corneoscleral limbus to dislocate the nucleus and tilt it up at the 12 o'clock position (Fig. 2). As the nucleus is being dislocated, two maneuvers

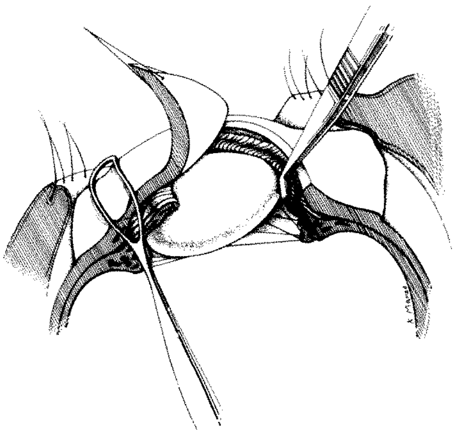

Fig. 2 (Evans). Closed forceps retract the iris so the superior pole of the nucleus can be tipped up over the iris where it may be either picked up or nudged out of the eye.

are possible. One may tilt the forceps back, still retracting the iris, to permit the nucleus to ride over the closed blades with the iris underneath, then slide the forceps from under the nucleus, and use it to nudge the nucleus out of the eye. This technique works best with large nuclei. Alternatively, the forceps are tilted back and the jaws opened to receive the dislocating nucleus, as it rides over the lower blade, which retracts the iris. Small nuclei may be delivered by this method. When the instrument is used in this manner, it is generally not necessary to exert any pressure on the eye near the incision to dislocate the nucleus, thereby protecting the integrity of the zonules in the area. The forceps shown in Figure 1 are for the right hand. Forceps for the left hand are a mirror image of this instrument.

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*The forceps were made by Karl Ilg Industries, Inc., St. Charles, Illinois.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Stability of Refraction During Four Years After Radial Keratotomy in the Prospective Evaluation of Radial Keratotomy Study

EDITOR:

The article, "Stability of refraction during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study," by G. O. Waring III and associates (Am. J. Ophthalmol. 111:33, February 1991), was of great interest. The study design, methods, and data-gathering techniques were superb and serve as an example of the authors' profound commitment to a comprehensive understanding of radial keratotomy. I commend them for their diligence.

The data raised several points of potential concern that can be analyzed under worst and best case situations. Consider the worst case first.

From six months to four years, the percentage of patients who have 1.0 diopter or greater hyperopic shift increased from 5.3% to 22.6%. There were no data to indicate that this trend was decreasing or self-limited. In other words, if the trend continues, 100% of patients would eventually have 1.0 diopter or more of hyperopic shift. For many patients, particularly those slightly undercorrected, this would be a welcome change, whereas others would become overcorrected.

The authors note that the average hyperopic shift over four years for the entire population studied was 0.4 diopter. Thus, roughly, there is 0.1 diopter of hyperopic shift per year. If this rate is constant, there would be approximately 1.0 diopter of hyperopic shift per decade. After 40 years, the average patient would have 4.0 diopters of hyperopic shift. Such a shift would be unwelcomed by most patients. The authors noted that patients with smaller optical zone sizes tended to have more hyperopic shift, which implies that some patients may be more profoundly affected than others.

The best case would be that in which the patient's refraction stabilized or that we could somehow control this shift to the patient's advantage (with patching or pharmacologic agents). Such an outcome would be reassuring to patients and physicians alike.

The most likely outcome for refractive errors in these patients probably lies somewhere between the worst and best case. However, we cannot predict the outcome without further detailed studies such as the one the Prospective Evaluation of Radial Keratotomy Study has provided. A study of longer duration is obviously needed so we can rationally advise our patients regarding the long-term safety and efficacy of radial keratotomy. I urge the study group to continue their work in this important area.

SCOTT MACRAE, M.D.
Portland, Oregon

Reply

EDITOR:

We thank Dr. MacRae for his observations and agree with him that a detailed study of the long-term efficacy and safety of radial keratotomy is needed. The PERK Study has been awarded funding by the National Eye Institute to obtain a clinical examination of patients in the study at approximately ten years after surgery. During 1991 and 1992 the Coordinating Centers will be engaged in tracking the location of study patients. The Clinical Centers will begin contacting patients in 1992 and preparing for patient examinations, which will be done during 1993. Data analysis and manuscript preparation will be done at the Coordinating Centers during 1994 and 1995 along with preparation for possible further follow-up of patients. This study will provide information on the intermediate to long-term stability of refractive error after radial keratotomy.

GEORGE O. WARING III, M.D.
AND THE PROSPECTIVE EVALUATION OF RADIAL KERATOTOMY STUDY GROUP

Anterior Chamber Aspirate Cultures After Uncomplicated Cataract Surgery

EDITOR:

The article, "Anterior chamber aspirate cultures after uncomplicated cataract surgery," by J. B. Dickey, K. D. Thompson, and W. M. Jay (Am. J. Ophthalmol. 112:278, September 1991), contains a flaw in methodology, which may account for the large percentage of patients with culture-positive anterior chamber aspirates. Antiseptic preparation consisted of hexachlorophene, followed by saline rinse, and finally povidone-iodine. This combination of cationic and anionic soaps creates neutralization of both preparation solutions, thereby negating their bacteriostatic and bacteriocidal effects.

It would be interesting for the authors to repeat their study, substituting either of the preoperative facial preparation agents individually to learn if the anterior chamber colony counts would drop further.

ROBERT T. MCBRATNEY, D.O.
Tulsa, Oklahoma

Reply

EDITOR:

Dr. McBratney is correct in his statement that the combination of cationic and anionic soaps creates neutralization of both detergents, thereby negating their antimicrobial properties. A well-known example of this principle occurs when the quaternary ammonium compound, benzalkonium chloride (a cationic antiseptic), is neutralized on exposure to the anionic detergent hexachlorophene.[1,2] However, both the iodine in the 5% povidone-iodine and the chloride in the 0.25% hexachlorophene used in our study were anionic in nature,[3] and in the form of solutions without soap. These anionic antiseptic solutions, povidone-iodine and hexachlorophene, are therefore supplied in an acidic medium, and their antibacterial activity would be expected to be reduced on exposure to cations in the alkali[1] (but not on exposure to other anions). The problem of ionic neutralization, therefore, does not exist between povidone-iodine and hexachlorophene, since they are both anions.

JAMES B. DICKEY, M.D.
KENNETH D. THOMPSON, Ph.D.
WALTER M. JAY, M.D.
Maywood, Illinois

References

1. Reynolds, E. F., Parfitt, K., Parsons, A. V., and Sweetman, S. C. (eds.): Martindale, The Extra Pharmacopoeia, ed. 29. London, The Pharmaceutical Press, 1989, pp. 949, 952, 963, and 1187.
2. McEvoy, G. K., and Litvak, K. (eds.): AHFS Drug Information, ed. 33. Bethesda, American Society of Hospital Pharmacists, Inc., 1991, pp. 2121–2123.
3. Siebring, B. R., and Schaff, M. E.: General Chemistry, ed. 1. Belmont, California, Wadsworth Inc., 1980, p. 145.

Isolated Neurofibromas of the Conjunctiva

EDITOR:

In the article, "Isolated neurofibromas of the conjunctiva," by P. H. Kalina, G. B. Bartley, G. Campbell, and H. Buettner (Am. J. Ophthalmol. 111:694, June 1991), Table 2 summarizes the published reports of isolated neurofibroma of the conjunctiva. The authors were making a case for the finding of systemic neurofibromatosis in the majority of patients who have isolated neurofibroma of the conjunctiva. In that table, they referred to isolated episcleral neurofibroma that occurred in a 22-year-old white woman who had had the lesion for at least seven years.

In that report I stated that there were no findings of systemic neurofibromatosis.[1] Four years later I learned, however, that the patient developed bilateral acoustic neuromas, and therefore, the case should be reclassified as neurofibromatosis type 2.

The late development of bilateral acoustic neuromas further supports systemic neurofibromatosis as an underlying factor in patients with an isolated neurofibroma of the conjunctiva. My case was especially remarkable because of a normal family history and the absence of neurofibromatosis. Four years later, however, the patient showed systemic signs. Thus, isolated congenital neurofibroma may represent the initial sign of systemic neurofibromatosis.

HENRY D. PERRY, M.D.
Rockville Centre, New York

Reference

1. Perry, H. D.: Isolated episcleral neurofibroma. Ophthalmology 89:1095, 1982.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Oftalmologia En Bolivia. Grupos Etnicos Aislados (Ophthalmology in Bolivia. Isolated Ethnic Groups). By Teodoro Aracena Ibarra. Bochabamba, Bolivia, Editorial Serrano, 1991. No price given

Reviewed by Aldo Fantin
Iowa City, Iowa

Dr. Aracena is an ophthalmologist with an interest in anthropology and archaeology. He has crisscrossed Bolivia many times, visiting isolated, inbred ethnic groups, to examine eyes and learn all he could about the history and customs of the various tribes.

He found that the paleo-amerindians (the oldest ethnic group in the Americas) have virtually no refractive errors, whereas many of the neo-amerindians and related groups have hyperopia.

He found pterygia to be unusually common among the Ese Ejja, and 40% of the Quechuas he examined had a myopic astigmia. Severe myopia was common in the Chimane, and some tapetoretinal degeneration was seen in the Yanahuaya. He saw chorioretinal scars everywhere, which he thought were toxoplasmic, and he believed the prevalence of color vision defects and glaucoma was astonishingly low in all groups.

Dr. Aracena also took the time to describe the disease-related mythology of these tribes and the popular medicines of plant-origin that were in common use. He also remarked on the discovery that pinhole devices were employed by precolombian cultures. This is a fascinating book.

Books Received

L'Annee Therapeutique et Clinique en Ophtalmologie, Volume XLI. By A. Dubois-Poulsen. Paris, Diffusion General de Librairie, 1990. 283 pages, index, illustrated. No price given.

This published group of papers on various ophthalmic topics (together with three detailed round-table discussions) offers a glimpse of the vigor of French ophthalmology.

Cataract Biochemistry Epidemiology and Pharmacology. By John Harding. New York, Chapman & Hall, Inc., 1991. 333 pages, index, illustrated. $139.95

Here is a little of everything you might possibly have wanted to know about cataracts except for how to manage them clinically. They book is not likely to become a bestseller amongst cataract surgeons. It is, however, well written, carefully edited, and a pleasure to read. The recent literature is critically reviewed and well documented. It will be a valuable source of references for several years.

From Pigments to Perception. Advances in Understanding Visual Processes. Edited by Arne Valberg and Barry B. Lee. New York, Plenum Publishing Corporation, 1991. 484 pages, index, illustrated. $120

This symposium, held in Norway in August 1990, demonstrates how specialists in psychophysics and physiology now work closely together in a joint effort to increase understanding of the visual system. The chapter titles include the following: Biophysics and Psychophysics and Photoreceptors; P-cell and M-cell Pathways and Psychophysics; Visual-Evoked Potentials; Cortical Processing and Psychophysical Measurement; Psychophysical Studies and Postreceptoral Processes; and Models, Neural Processes, and Psychophysics.

Medikamentose Augentherapie, ed. 3. By Paul U. Fechner and Klaus D. Teichmann. Stuttgart, Germany, Ferdinand Enk Verlag, 1991. 366 pages, index, illustrated. No price given.

This new edition of a popular German language text on drugs and the eye encompasses the literature through 1990.

Ocular Histopathology. A Guide to Differential Diagnosis. By Curtis E. Margo and Hans E.

Grossniklaus. Philadelphia, W. B. Saunders, 1991. 340 pages, index, illustrated. $89

How a histopathologist uses morphology to solve problems and determine a diagnosis is the topic of this text, which is illustrated with eye diseases. It is primarily an eyes-to-the-microscope exercise, with the clinical history withheld until the differential diagnosis list needs some trimming down. It should be a valuable teaching tool.

A Text and Atlas of Strabismus Surgery. By Renee Richards, Steven Greenberg, and J. Thomas Herbert. Baltimore, Williams & Wilkins, 1991. 226 pages, index, illustrated. $150

This text is based on a series of lectures for residents that reflect the authors' preferred, generally conservative, approach to strabismic disorders. For each major disorder, a clear rationale for treatment choice is provided, which is particularly useful to the beginning strabismus surgeon. Especially helpful are the detailed descriptions of the surgical techniques and their accompanying color photographs. A separate section offers tips on surgery, advice on preoperative counseling, and anesthesia considerations.

Year Book of Ophthalmology 1991. Edited by Peter R. Laibson. St. Louis, Mosby Year Book, 1991. 292 pages, index, illustrated. $57.95

For those of us who are having trouble keeping up with our journals, this hardcover annual review of ophthalmology should be just the thing. The papers were chosen, summarized, and then discussed with intelligence and sensitivity by members of the Wills Faculty Editorial Board. The harried ophthalmologist should be grateful.

ABSTRACT DEPARTMENT

Edited by Ronald M. Burde, M.D.

Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. Kjeldsen-Kragh, J.*, Haugen, M., Borchgrevink, C. F., Laerum, E., Eek, M., Mowinkel, P., Hovi, K., and Forre, O.: Lancet 338:899, 1991.

Fasting is an effective treatment for rheumatoid arthritis, but most patients relapse on reintroduction of food. The effect of fasting followed by one year of vegetarian diet was assessed in a randomized, single-blind controlled trial. 27 patients were allocated to a four-week stay at a health farm. After an initial 7–10 day subtotal fast, they were put on an individually adjusted gluten-free vegan diet for 3–5 months. The food was then gradually changed to a lactovegetarian diet for the remainder of the study. A control group of 26 patients stayed for four weeks at a convalescent home, but ate an ordinary diet throughout the whole study period. After four weeks at the health farm the diet group showed a significant improvement in number of tender joints, Ritchie's articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, erythrocyte sedimentation rate, C-reactive protein, white blood cell count, and a health assessment questionnaire score. In the control group, only pain score improved significantly. The benefits in the diet group were still present after one year, and evaluation of the whole course showed significant advantages for the diet group in all measured indices. This dietary regimen seems to be a useful supplement to conventional medical treatment of rheumatoid arthritis.—Authors' abstract

*Institute of Immunology and Rheumatology, National Hospital, Fredrikke Qvams gate 1,0172 Oslo, Norway.

Rapid recovery from cortical visual impairment following correction of prolonged shunt malfunction in congenital hydrocephalus. Connolly, M. B., Jan, J. E.*, and Cochrane, D. D.: Arch. Neurol. 48:956, 1991.

Three children with congenital hydrocephalus are described in whom increased intracranial pressure was associated with severe, long-lasting cortical visual impairment. Following shunt revisions or reconstructive craniotomies, visual improvement began within hours. It is speculated that increased intracranial pressure can occasionally result in chronic hypoperfusion of the parietal-occipital lobes, either due to posterior cerebral artery compromise secondary to transtentorial pressure gradient or to direct compression of cerebral tissues.—Authors' abstract

*Visually Impaired Program, British Columbia's Children's Hospital, 4480 Oak St., Vancouver, British Columbia, Canada V6H 3V4.

N-Methyl-D-Aspartate antagonists in the treatment of Parkinson's disease. Greenamyre, J. T.*, and O'Brien, C. F.: Arch. Neurol. 48:977, 1991.

Current long-term treatment of Parkinson's disease is inadequate, and improved symptomatic and neuroprotective therapies are needed. Recent interest has focused on the use of antagonists of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor in Parkinson's disease. Abnormally increased activity of the subthalamic nucleus is postulated to play a central pathophysiological role in the signs of Parkinson's disease, and NMDA antagonists may provide a means of decreasing this activity selectively. Like dopaminergic agonists, NMDA antagonists can reverse the akinesia and rigidity associated with monoamine depletion or neuroleptic-induced catalepsy. Very low doses of NMDA antagonists markedly potentiate the therapeutic effects of dopaminergic agonists. There is evidence that the beneficial effects of anticholinergic drugs and amantadine may be mediated, in part, by NMDA receptor blockade. Moreover, NMDA antagonists provide profound protection of dopaminergic neurons of the substantia nigra in the MPTP (1-methyl-r-phenyl-1,2,3,6-tetrahydropyridine) and methamphetamine models of Parkinson's disease. The clinical use of NMDA antagonists may prove useful in Parkinson's disease to treat symptoms and retard disease progression.—Authors' abstract

*Department of Neurology, University of Rochester Medical Center, 601 Elmwood Ave., Box 673, Rochester, NY 14642.

The T-cell proliferative assay in the diagnosis of Lyme disease.

Dressler, F., Yoshinari, N. H., and Steere, A. C.*: Ann. Intern. Med. 115:533, 1991.

Objective: To determine the sensitivity and specificity of the T-cell proliferative assay as a diagnostic test in Lyme disease. *Design*: Cross-sectional study of patients with Lyme arthritis or chronic neuroborreliosis who had a history of erythema migrans, positive antibody responses to *Borrelia burgdorferi* by enzyme-linked immunosorbent assay (ELISA), or both; patients with other diseases; and healthy subjects. *Setting*: Diagnostic Lyme disease clinic in a university hospital. *Patients*: Forty-two of the 67 patients with active Lyme arthritis or chronic neuroborreliosis who were seen during the study period; 16 patients with inactive late Lyme disease; 77 patients with other rheumatologic or neurologic diseases; 9 workers from the Borrelia laboratory; and 9 healthy subjects. *Measurements and Main Results*: Nineteen of 42 patients with Lyme arthritis or chronic neuroborreliosis and 4 of 77 patients with other diseases had positive T-cell proliferative responses to *B. burgdorferi* antigens. The sensitivity of the proliferative assay was 45% (95% CI, 30% to 60%) and the specificity was 95% (95% CI, 87% to 99%). Twelve of 27 patients with active Lyme arthritis, 7 of 15 patients with chronic neuroborreliosis, 4 of 16 patients with inactive Lyme disease, 4 of 9 healthy Borrelia laboratory workers, and 0 of 9 healthy subjects had positive responses. Three of five patients with Lyme disease who had negative or indeterminant antibody responses by ELISA had positive T-cell proliferative responses. *Conclusion*: The T-cell proliferative assay may be a helpful diagnostic test in the small subset of patients with late Lyme disease who have negative or indeterminant antibody responses by ELISA.—Authors' abstract

*Division of Rheumatology, New England Medical Center, NEMC 406, 750 Washington St., Boston, MA 02111.

Sleep apnea in acromegaly.

Grunstein, R. R.*, Ho, K. Y., and Sullivan, C. E.: Ann. Intern. Med. 115:527, 1991.

Objective: To provide information on the nature, prevalence, and severity of sleep apnea in patients with acromegaly. *Design*: Consecutive case series. *Setting*: Tertiary referral hospital. *Patients*: Fifty-three patients with acromegaly were consecutively referred: 33 patients were referred because of clinical suspicion of sleep apnea and 20 patients were referred without suspected apnea. *Measurements*: Sleep studies as well as growth hormone and insulin-like growth factor 1 (IGF-1) measurements were done. *Main Results*: Thirty-one patients (93%; 95% CI, 85% to 100%) referred because of suspicion of sleep apnea had sleep apnea compared with 12 patients (60%; CI, 37% to 83%) referred without suspected sleep apnea. Patients with sleep apnea did not have biochemical evidence of increased disease activity (random growth hormone, 12.7 ± 4.4 μg/L; mean growth hormone at 24-hour sampling, 10.8 ± 8.4 μg/L; IGF-1, 90.0 ± 7.5 nmol/L) compared with patients without sleep apnea (random growth hormone, 14.2 ± 4.9 μg/L, $P > 0.2$; IGF-1, 90.0 ± 10.0 nmol/L, $P > 0.2$). Central sleep apnea was the predominant type of apnea in 33% (CI, 18% to 47%) of patients and was associated with higher random growth hormone and IGF-1 levels than was obstructive apnea (random growth hormone, 23.4 ± 3.9 compared with 8.8 ± 3.1 μg/L, $P < 0.001$; IGF-1, 126 ± 17.5 compared with 72.5 ± 7.5 nmol/L, $P < 0.01$). *Conclusions*: Sleep apnea is common in acromegaly. The rate of central sleep apnea was unexpectedly high in patients with acromegaly, and biochemical evidence of increased disease activity was associated with the presence of central apnea rather than with the degree of sleep apnea. Altered respiratory control is a possible mechanism producing sleep apnea in acromegaly.—Authors' abstract

*Sleep Disorders Centre, Royal Prince Alfred Hospital, Missenden Rd., Camperdown, Sydney, New South Wales, 2050 Australia.

VEP projections in congenital nystagmus; VEP asymmetry in albinism: a comparison study.

Apkarian P.*, and Shallo-Hoffmann, J.: Invest. Ophthalmol. Vis. Sci. 32:2653, 1991.

Visual evoked potential (VEP) asymmetry in which a preponderance of nasal and temporal retina afferents project to the contralateral hemisphere after full-field monocular stimulation is considered specific to albinism. Some reports, however, suggest that patients with congenital nystagmus (CN) share the albino-like visual pathway anomaly. To examine the clinical specificity of albino misrouting, VEP topography was assessed in ten patients with congenital nystagmus and in ten age-matched albino patients. As an additional control, the VEP response profiles from eight albino patients with no nystagmus were also evaluated. The results are definitive; VEP contralateral asymmetry reflecting temporal retinal misprojection is evinced only in albino patients. Furthermore, ocular-motor instabilities in CN cannot be readily attributed to albino-type misrouted retinal-cortical projections.—Authors' abstract

*Academic Medical Center, Ophthalmology Department-A2, Meibergdreef 9, 1105 AZ Amsterdam ZO, The Netherlands.

Recurrent attacks of amaurosis fugax treated with calcium channel blocker. Winterkorn J. M. S.*, and Teman, A. J.: Ann. Neurol. 30:423, 1991.

Vasospasm may be one of the causes of amaurosis fugax. A patient is reported who daily experienced multiple brief episodes of amaurosis fugax. The absence of physical, laboratory, or radiographic evidence for thromboembolism, hemodynamic compromise, or vasculitis, suggested that the amaurosis might be caused by vasospasm. This hypothesis was supported by cessation of the attacks of amaurosis when the patient was treated with a calcium channel blocker.—Authors' abstract

*North Shore University Hospital, Cornell University Medical College, Department of Ophthalmology, 300 Community Dr., Manhasset, NY 11030.

Characterization of a murine model of recurrent herpes simplex viral keratitis induced by ultraviolet B radiation. Laycock, K. A., Lee, S. F., Brady, R. H., and Pepose, J. S.*: Invest. Ophthalmol. Vis. Sci. 32:2741, 1991.

The authors characterized a murine model of herpes simplex virus (HSV) reactivation in which recurrent herpetic keratitis was obtained in up to 80% of animals. Five weeks after ganglionic latency was established in National Institutes of Health inbred mice after corneal inoculation, HSV type 1 (HSV-1) was reactivated by irradiating the previously inoculated eye with ultraviolet (UV) light. Comparison of different UV wavelengths showed UVB to be optimal for reactivation, with peak viral recurrence being induced by a total exposure of approximately 250 mJ/cm^2. Reactivated infectious virus generally began to appear in trigeminal ganglia 2 days postirradiation and was subsequently detectable in the cornea by both corneal swabbing and immunostaining for viral antigens. Two consecutive outbreaks of viral recurrence at the ocular surface were induced in selected animals by serial exposure to UVB. Advantages of this model over other models of recurrent keratitis are discussed.—Authors' abstract

*Department of Ophthalmology, Box 8096, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

Lupus anticoagulants, anticardiolipin antibodies, and fetal loss: a case-control study. Infante-Rivard, C.*, David, M., Gauthier, R., and Rivard, G. E.: N. Engl. J. Med. 325:1063, 1991.

Background. Lupus anticoagulants and anticardiolipin antibodies are antiphospholipid antibodies that have been associated with fetal loss, but they have not been shown unequivocally to be a risk factor for this event. *Methods.* To estimate the risk of fetal loss in association with these antibodies, we conducted a hospital-based case-control study of 331 women with spontaneous abortion or fetal death (case patients) and 993 controls. The subjects were included in the study only if they reported that they had had no previous spontaneous fetal loss. Each control was a pregnant woman who, in the same period of pregnancy as a case patient, had not had a fetal loss. Lupus anticoagulants were identified in blood samples through a series of coagulation tests, and IgG anticardiolipins by an enzyme-linked immunosorbent assay. Each subject was interviewed in person to obtain information on potential confounding variables, such as sociodemographic characteristics and medical conditions. *Results.* Lupus anticoagulants were found in blood from 17 case patients (5.1 percent) and 38 controls (3.8 percent). The crude odds ratio for the association between lupus anticoagulants and fetal loss was 1.35 (95 percent confidence interval, 0.75 to 2.43); the odds ratio adjusted for confounders was 1.42 (95 percent confidence interval, 0.72 to 2.80). An IgG anticardiolipin level of 5 units or more was found in 4 case patients (1.2 percent) and 15 controls (1.5 percent). The crude and adjusted odds ratios for fetal loss were 0.80 (95 percent confidence interval, 0.26 to 2.41) and 1.28 (95 percent confidence interval, 0.38 to 4.21), respectively. *Conclusions.* There is no apparent justification for considering lupus anticoagulants or IgG anticardiolipins to be risk factors for fetal loss among women who present with spontaneous abortion or fetal death and have had no previous spontaneous fetal loss.—Authors' abstract

*School of Occupational Health, McGill University, 1130 Pine Ave. W., Montreal, PQ H3A 1A3, Canada.

Unilateral oculomotor palsy and bilateral ptosis from paramedian midbrain infarction. Liu, G. T., Carrazana, E. J., and Charness, M. E.*: Arch. Neurol. 48:983, 1991.

Lesions of the oculomotor fascicles are localized clinically by associated neurologic deficits. We present two patients with bilateral ptosis, unilateral paresis of all other muscles innervated by the oculomotor nerve, and sparing of the contralateral superior rectus muscle—findings suggesting a lesion of the proximal oculomotor fascicles and the central caudal subnucleus. To our knowledge, these are the first such cases with radiologic confirmation of a lesion within the dorsal, paramedian midbrain.—Authors' abstract

*Section of Neurology (127), Brockton-West Roxbury Veterans Affairs Medical Center, 1400 VFW Pkwy., West Roxbury, MA 02132.

The time course of interocular suppression in normal and amblyopic subjects. de Belsunce, S., and Sireteanu, R.*: Invest. Ophthalmol. Vis. Sci. 32:2645, 1991.

The authors measured the time course of interocular suppression of five normal subjects and eleven patients with amblyopia (strabismic and/or anisometropic). Orthogonal gratings were presented dichoptically for durations that ranged from 10–6000 msec. All normal observers reported fusion or superimposition of the orthogonal gratings for short stimuli and reported binocular rivalry for stimuli longer than 150 msec. At long presentation times, all amblyopes constantly suppressed the pattern that was presented to their amblyopic eye. Six amblyopes showed superimposition of the two patterns at short presentation times. Of these, three had time courses similar to those of normal observers; the other three had a much shorter onset of suppression (about 80 msec). The remaining five amblyopes perceived only the pattern of the dominant eye at short stimulus durations; at intermediate durations, they reported partial superimposition of the stimuli, whereas at the longest stimulus durations, again only the stimulus of the dominant eye was perceived.

The results suggest that binocular rivalry in normal observers and strabismic suppression in amblyopes are mediated by different mechanisms. The heterogeneity of the time courses of suppression in amblyopes might result from differences in the disturbances of early visual development (age at onset of strabismus and/or anisometropia, origin, and therapy).—Authors' abstract

*Max-Planck-Institut für Hirnforschung, Deutschordenstr. 46,6000 Frankfurt 71, Germany.

Tissue distribution of type VIII collagen in human adult and fetal eyes. Tamura, Y., Konomi, H.*, Sawada, H., Takashima, S., and Nakajimo, A.: Invest. Ophthalmol. Vis. Sci. 32:2636, 1991.

The type VIII collagen tissue distribution in human adult (32–78 yr of age) and fetal (16–27 weeks of gestation) eyes was studied immunohistochemically using a monoclonal antibody to type VIII collagen. Type VIII collagen was distributed in a linear or fibrous fashion in adult eyes in Descemet's membrane of the cornea, the trabecular meshwork, the walls of Schlemm's canal, Bruch's membrane, the choroidal stroma, the sclera, the cribriform plates of the optic nerve, and the intima of the central retinal artery. The staining in the central retinal artery was similar to that of type IV collagen. No distinct positive staining was seen in other blood vessels. When fetal eyes were examined, significant differences in positive staining were found between adults and fetuses in the sclera. In fetal eyes, the posterior sclera was strongly stained; however, the positive staining gradually decreased, and in the equatorial area it disappeared. The cribriform plates of the lamina cribrosa and the presumptive Bruch's membrane in fetal eyes did not react with the antibody. The trabecular meshwork and Descemet's membrane, but no other part of anterior section of fetal eyes, reacted with the antibody.—Authors' abstract

*Division of Mental Retardation and Birth Defect Research, National Institute of Neuroscience, NCNP, 4-1-1 Ogawahigashi-machi, Kodaira-shi, Tokyo 187, Japan.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

International Society for Genetic Eye Diseases and International Symposium on Retinoblastoma: Joint Meeting

The IX Meeting of the International Society for Genetic Eye Diseases and the VI International Symposium on Retinoblastoma are scheduled for May 28–30, 1992, in Siena, Italy. This joint meeting will follow the IX Congress of the European Ophthalmological Society in Brussels May 23—28, 1992. For more information, write Irene H. Maumenee, M.D., Wilmer Institute, Johns Hopkins Hospital, 600 N. Wolfe St., 321 Maumenee Bldg., Baltimore, MD 21205; telephone (301) 955-5214.

Second International Symposium on Ocular Trauma

The Second International Symposium on Ocular Trauma will be April 2–5, 1992, in Geneva, Switzerland. For further information, write The Secretariat, 2nd International Symposium on Ocular Trauma, Kuoni Travel Ltd., 7 rue de Berne, P.O. Box 1731, CH 1211 Geneva 1, Switzerland; fax 0041-22-7315078.

Cedars Sinai Medical Center: Genetic Diseases and the Eye Course

The Division of Ophthalmology of the Cedars Sinai Medical Center will sponsor a one-day course on Genetic Diseases and the Eye Jan. 25, 1992. For additional information, write Yaron Rabinowitz, M.D., Cornea-Genetic Eye Medical Clinic, 600 Mark Goodson Bldg., Cedars Sinai Medical Center, 444 S. San Vicente Blvd., Los Angeles, CA 90048; telephone (213) 855-2613.

The Emory Clinic: 29th Annual Emory-Grady Alumni Postgraduate Ophthalmology Conference

The Emory University School of Medicine will sponsor the 29th Annual Emory-Grady Alumni Postgraduate Ophthalmology Conference Jan. 31–Feb. 1, 1992, in Atlanta, Georgia. For additional information, write the Office of Continuing Medical Education, Emory University School of Medicine, 1440 Clifton Rd., Atlanta, GA 30322; telephone (404) 727-5695.

Good Samaritan Medical Center: Corneal Diseases Conference

The Good Samaritan Medical Center of West Palm Beach will sponsor a course, Current Corneal Concepts, Feb. 15 and 16, 1992, in West Palm Beach, Florida. For further information, write the Continuing Medical Education Department, Good Samaritan Medical Center, P.O. Box 3166, West Palm Beach, FL 33402; telephone (407) 650-6236.

University of Louisville: 20th C. Dwight Townes Memorial Seminar

The Department of Ophthalmology and Visual Sciences at the University of Louisville School of Medicine will hold its 20th C. Dwight Townes Memorial Seminar March 27 and 28, 1992, in Louisville, Kentucky. For more information, write Nancy Rodman, 301 E. Muhammad Ali Blvd., Louisville, KY 40202; telephone (502) 588-5466.

Manhattan Eye, Ear & Throat Hospital: Glaucoma Seminar

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a Glaucoma Seminar (live-televised surgery) Feb. 29, 1992, in New York City. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Manhattan Eye, Ear & Throat Hospital: Frontiers in Vitreoretinal and Laser Surgery

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold the Frontiers in Vitreoretinal and Laser Surgery

Course March 7, 1992, in New York City. For additional information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

North Carolina Society of Ophthalmology: Annual Meeting

The North Carolina Society of Ophthalmology will hold its annual meeting, entitled Focus on Diabetes 2,000, April 23–25, 1992, in Asheville, North Carolina. For further information, write Carol Russell, NCSO, P.O. Box 27167, Raleigh, NC 27611; telephone (919) 833-3836.

Ohio State University College of Medicine: 35th Annual Postgraduate Symposium in Ophthalmology

The Ohio State University College of Medicine will sponsor the 35th Annual Postgraduate Symposium in Ophthalmology: Diabetes Mellitus—Ophthalmic Perspectives March 6 and 7, 1992, in Columbus, Ohio. For more information, write the Continuing Medical Education Office, Rm. A352, Starling-Loving Hall, 320 W. 10th Ave., Columbus, OH 43210; telephone (800) 492-4445.

Pittsburgh Ophthalmology Society: Spring Meeting

The Pittsburgh Ophthalmology Society will hold its Spring Meeting March 20 and 21, 1992, in Pittsburgh. Alan B. Scott of San Francisco will deliver the Annual Harvey Thorpe Lecture. For more information, write Pat Kennerdell, 2545 Mosside Blvd., Monroeville, PA 15146; telephone (412) 243-8845.

Rush Medical College: Ophthalmology Clinical Review Course

The annual Rush Medical College Ophthalmology Clinical Review Course will be held March 13–15 and 20–22, 1992, at Rush-Presbyterian-St. Luke's Medical Center in Chicago. For additional information, write the Office of Continuing Medical Education, Rush Medical College, 600 S. Paulina, Chicago, IL 60612; telephone (312) 942-7119.

Walter Reed Army Medical Center: 14th Ophthalmology Postgraduate Course

The Walter Reed Army Medical Center will sponsor the 14th Ophthalmology Postgraduate Course March 23 and 24, 1992, in Bethesda, Maryland. For more information, write Ms. Coleman, Ophthalmology Service, Rm. 1F14, Walter Reed Army Medical Center, Washington, D.C. 20307-5001.

Washington National Eye Center: Annual Symposium

The Washington National Eye Center and the Department of Ophthalmology of the Washington Hospital Center Annual Symposium, Diagnosis and Management of Grave's Disease, will be held March 6 and 7, 1992, in Washington, D.C. For more information, write Penelope A. Helfgott, WNEC, Ste. 6B-13, 110 Irving St. N.W., Washington, D.C. 20010-2975; telephone (202) 877-6982.

Medical College of Wisconsin: Evaluation and Management of Uveitis

The Medical College of Wisconsin will sponsor Evaluation and Management of Uveitis Feb. 15, 1992, in Milwaukee, Wisconsin. For additional information, write J. Werner, M.D., Eye Institute, 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5353.

Wilmer Ophthalmological Institute: Current Concepts in Ophthalmology and Hands-on Phacoemulsification Wet Lab

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor the 14th Annual Current Concepts in Ophthalmology and Hands-on Phacoemulsification Wet Lab Feb. 9–16, 1992, in Dorado, Puerto Rico. For more information, write the Program Coordinator, Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 20, Baltimore, MD 21205-2195; telephone (301) 955-2959.

Minnesota Academy of Ophthalmology: 1991–1992 Officers

Richard P. Carroll has been elected president of the Minnesota Academy of Ophthalmology for 1991–1992. Other officers elected are Martin B. Kaplan president-elect; Rene W. Pelletier treasurer; and Jerry L. Kobrin secretary. Raymond C. Croissant continues as chairman of the External Affairs Committee, and Paul T. Wicklund has been appointed chairman of the Internal Affairs Committee.

Pittsburgh Ophthalmology Society: 1991–1992 Officers

The Pittsburgh Ophthalmology Society has elected new officers for 1991–1992: John S. Kennerdell, president; William J. McVay, vice president; Peter J. Berkowitz, secretary; and John M. Mikulla, treasurer.

Fight for Sight: 1992 Awards Program

The Fight for Sight Research Division of the National Society to Prevent Blindness has announced the awards program for 1992–1993. The programs include Grants-in-Aid fund studies of priority interest and pilot projects with a maximum annual award of $12,000; Postdoctoral Fellowships with a maximum annual award of $14,000; and Student Fellowships for summer research with awards of $500 per month for a maximum of three months. The closing date for receipt of applications is March 1, 1992. For further information and applications, write Fight for Sight Research Division, National Society to Prevent Blindness, 500 E. Remington Rd., Schaumburg, IL 60173; telephone (708) 843-2020; fax (708) 843-8458.

Personals

Dan B. Jones

Dan B. Jones has been appointed to the Margarett Root Brown Chair of Ophthalmology at Baylor College of Medicine in Houston, Texas. Jones is the Sid W. Richardson Professor and Chairman of the Department of Ophthalmology. He joined the Baylor faculty in 1972 as an associate professor. Previously, he held positions at the Vanderbilt University School of Medicine and the University of Miami School of Medicine. He is currently chief of the ophthalmology service at the Methodist Hospital and at Ben Taub General Hospital.

C. P. Wilkinson

C. P. Wilkinson, Clinical Professor of Ophthalmology at the Dean McGee Eye Institute of the University of Oklahoma received the Heed Award during the 1991 meeting of the American Academy of Ophthalmology and the Pan American Association of Ophthalmology. Dr. Wilkinson received this award in recognition of his leadership and contributions to the field of ophthalmology. The award was presented by Dr. Bradley Straatsma, chairman of the Board of Directors of the Heed Foundation.

Dr. Wilkinson was a Heed Fellow in 1970–1971 at the Bascom Palmer Eye Institute at the University of Miami.

Clinical Characteristics Associated With Orbital Invasion of Cutaneous Basal Cell and Squamous Cell Tumors of the Eyelid

Gene R. Howard, M.D., Jeffrey A. Nerad, M.D., Keith D. Carter, M.D.,
and Duane C. Whitaker, M.D.

Over a six-year period, between 1984 and 1990, 622 patients with basal cell and squamous cell carcinoma of the eyelids were examined at our institution. Thirteen patients had orbital invasion at initial examination. The average age of patients at orbital invasion was 75.8 years. Ten patients were men, eight of whom had basal cell carcinoma and two of whom had squamous cell carcinoma. Most patients had an orbital mass and incomitant strabismus at initial examination. Invasive basal cell carcinoma developed in 11 patients, and squamous cell carcinoma developed in two patients. Ten patients were treated for cutaneous carcinoma at the site of invasion before examination at our institution. The average duration between onset of a cutaneous lesion and our examination for orbital invasion was 9.8 years for basal cell carcinoma and one year for squamous cell carcinoma. Radiologic and histopathologic features were reviewed. The clinical characteristics of these patients were reviewed and orbital exenteration was recommended to all 13 patients. Nine patients underwent exenteration and four refused the operation.

THE PERIOCULAR AREA is a common site for skin carcinomas. Today most skin cancers of the face are diagnosed when small and are cured with surgical excision. However, a threat to vision and life remains in a few patients who develop orbital invasion. In these patients cure is only possible with exenteration. In some patients, despite radical operations and sacrifice of the eye and orbital contents, cure is not possible and a threat to life by intracranial extension continues.

We identified 13 patients from a large series of patients (622 patients) with periocular basal cell carcinoma and squamous cell carcinoma in an attempt to identify the characteristics of these patients. Our goal in doing so was threefold. First, recognition that periocular skin cancer represents a potentially blinding and life-threatening disease is essential to the care of these lesions. Second, once orbital invasion is noted, early intervention, often with radical procedures, is necessary to prevent intracranial spread. Third, identification of patients at risk for orbital invasion may encourage aggressive management and care before growth of the cancer into the orbit.

Subjects and Methods

Thirteen patients with orbital invasion from basal cell or squamous cell carcinoma were identified (Table) and reviewed from 622 consecutive patients with eyelid tumors seen in the Departments of Ophthalmology and Dermatology during a six-year period from 1984 to 1990. Patients with periocular sebaceous cell carcinoma were excluded. Each patient underwent a complete ophthalmic and dermatologic examination. Radiologic imaging, including computed tomography or magnetic resonance imaging scans, were performed on all patients. Ten patients underwent excision of the cutaneous car-

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Accepted for publication Nov. 13, 1991.

From the Oculoplastic and Orbital Surgery Service (Drs. Howard, Nerad, and Carter), Department of Ophthalmology and Department of Dermatology (Dr. Whitaker), University of Iowa Hospitals and Clinics, Iowa City, Iowa. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Jeffrey A. Nerad, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

TABLE
SUMMARY OF PATIENT DATA

	TUMOR SIZE (CM^2)						
CASE NO., AGE (YRS), GENDER	BEFORE MOHS' TECHNIQUE	AFTER MOHS' TECHNIQUE	TUMOR LOCATION	DURATION OF TUMOR (YRS)	HISTOLOGIC PATTERN	INITIAL FINDINGS	RADIOLOGIC STUDIES
1, 73, M	0.4	8.9	Left lower eyelid, left medial canthus	10	Morphea	Mass	Computed tomography; soft-tissue mass, no bone erosion
2, 78, F	0.5	18.0	Right medial canthus	5	Basosquamous	Mass	Computed tomography; soft-tissue mass, no bone erosion
3, 54, M	0.72	56.0	Left lower eyelid	18	Basosquamous	Mass, strabismus	Magnetic resonance imaging; soft-tissue mass, no bone erosion
4, 75, M	No Mohs' microsurgery		Left lateral canthus	4	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, no bone erosion
5, 85, M	0.96	15.8	Right lower eyelid, right lateral canthus	5	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, no bone erosion
6, 68, M	2.3	15.0	Right medial canthus	7	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, no bone erosion
7, 71, M	3.0	6.3	Right lower eyelid	15	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, bone erosion
8, 86, F	1.0	8.4	Left lateral canthus	14	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, no bone erosion
9, 82, F	0.12	33.6	Left medial canthus	1	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, no bone erosion
10, 92, M	No Mohs' microsurgery		Left lower eyelid	10	Morphea	Mass, strabismus	Computed tomography; soft-tissue mass, bone erosion
11, 69, M	0.75	14.0	Right upper eyelid	10	Morphea	Mass	Computed tomography; soft-tissue mass, bone erosion
12, 70, M	12.0	75.0	Right lower eyelid	1	Squamous cell carcinoma	Mass, strabismus	Computed tomography; soft-tissue mass, bone erosion
13, 82, M	4.0	29.7	Left lateral canthus	1	Squamous cell carcinoma	Mass, strabismus	Magnetic resonance imaging; soft-tissue mass, bone erosion

*NA indicates not applicable.

cinoma in which the surgeons used Mohs' microsurgery. One patient underwent Mohs' microsurgery without obtaining free margins and refused exenteration. Three patients refused operations other than a cutaneous incisional biopsy. Radiologic and histopathologic studies of all patients were reviewed.

Case Reports

The following four cases are representative of the diversity of clinical signs and symptoms at initial examination, treatment, and outcome found in our study.

TABLE *(Continued)*
SUMMARY OF PATIENT DATA

PREVIOUS TREATMENT	TREATMENT	MARGINS OF RESECTION	FOLLOW-UP (YRS)	RECURRENCE*
Multiple excisions	Exenteration	Clear	7	No
Cryotherapy, radiation	Refused exenteration	Not clear	4	NA
Multiple excisions	Exenteration; radiation (6,400 cGy)	Not clear	1	NA
Multiple excisions	Refused exenteration; radiation (6,000 cGy)	None	3	NA
No treatment	Exenteration	Clear	7	No
One excision	Exenteration	Clear	4	No
No treatment	Exenteration	Clear	2	No
One excision, radiation	Refused treatment	None	2, deceased	NA
Multiple excisions	Exenteration	Clear	2	No
No treatment	Refused exenteration; radiation (6,800 cGy)	None	1	NA
Multiple excisions	Exenteration	Clear	1	No
One excision, radiation	Exenteration	Clear	1	No
Multiple excisions	Exenteration	Not clear	1, deceased	NA

Case 1

A 73-year-old white man with a left lower eyelid and left medial canthal mass was admitted to our institution in 1984. He had undergone multiple excisions elsewhere for recurrent basal cell carcinoma on the left lower eyelid during the preceding ten years. The medial examination showed a thickened lower eyelid with ectropion (Fig. 1, top). Ocular motility was normal. A computed tomographic scan showed thickening of the medial canthus without bone erosion. A biopsy showed morphea basal cell carcinoma. An extensive Mohs' microsurgical resection was completed that showed tumor infiltration of the medial canthal periosteum, medial rectus muscle, and surrounding orbital fat (Fig. 1, middle). Exenteration was recommended and performed in 1984. The margins of resection were clear. A follow-up examination seven years later showed no evidence of recurrence (Fig. 1, bottom).

Case 2

A 78-year-old white woman with a ten-year history of a right medial canthal lesion was examined at our institution in 1987. She had a 1.0 × 0.5-cm ulcerated mass that appeared to be fixed to the underlying bone at initial examination (Fig. 2, top). This region was treated elsewhere with multiple excisions in its early course, with cryotherapy on two occasions in 1986, and with radiotherapy seven months before our examination. She had normal ocular motility. A computed tomographic scan showed serpiginous thickening of the naso-orbital margin without bone erosion. Basal cell carcinoma was confirmed by biopsy. Mohs' microsurgery disclosed extensive periosteal involvement in the medial canthal region and medial orbital wall (Fig. 2, middle). Orbital exenteration was recommended, but was declined by the patient. She was treated with further local excision of the medial canthal region, removal of the anterior portion of the medial orbital wall and periosteum, succeeded by liquid nitrogen treatment of surrounding bone and soft tissue. The margins of resection were clear. Recurrence was not evident after four years of follow-up (Fig. 2, bottom).

Case 3

A 54-year-old white man was first examined in our clinic in 1990 for a recurrent basal cell carcinoma of the left lower eyelid. He had undergone multiple resections elsewhere for basal cell carcinoma in this region during the previous 18 years. On examination he had a solid indurated lower eyelid mass with a 0.9 × 0.8-cm ulceration, elevation of the left globe, and incomitant strabismus (Fig. 3, top left). A magnetic resonance imaging scan showed an inferior orbital soft-tissue mass with involvement of the inferior rectus muscle (Fig. 3, bottom right). Basal cell carcinoma was confirmed by biopsy. Mohs' microsurgery disclosed tumor extension into periosteal tissue and the infraorbital nerve. An exenteration was performed (Fig. 3, bottom left); however, surgical margins showed invasion of the infraorbital nerve at the orbital apex. A second neurosurgical procedure showed unresectable positive margins in the trigeminal ganglion. The patient received 6,400 cGy of postoperative radiation. Magnetic reso-

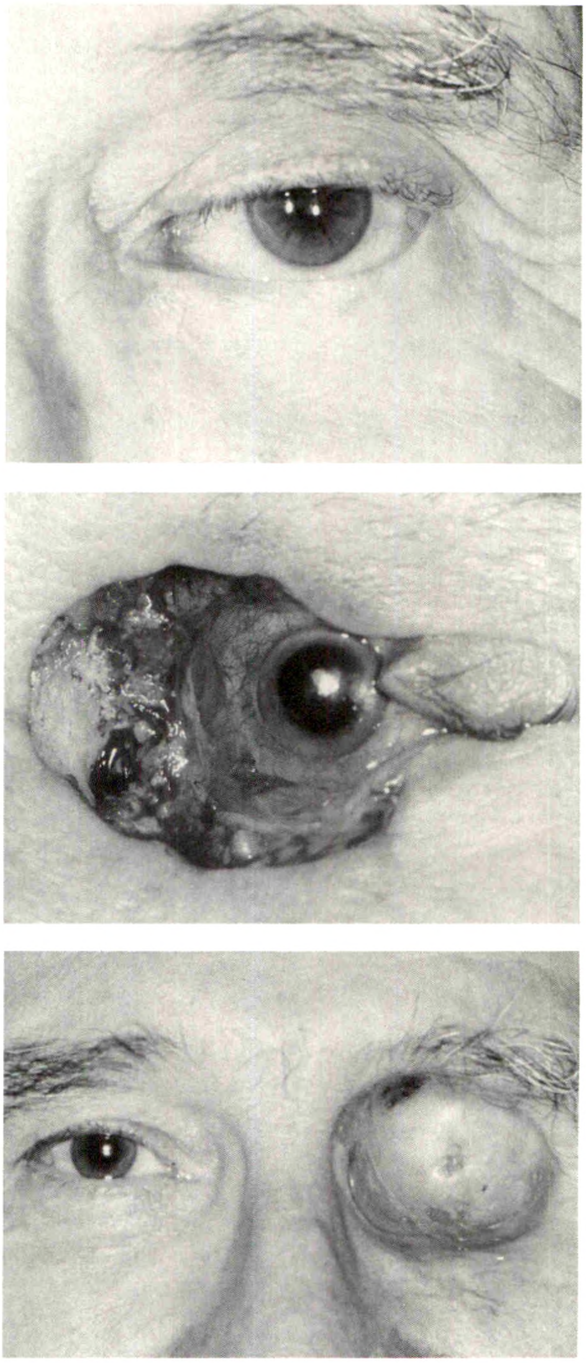

Fig. 1 (Howard and associates). Case 1. A 73-year-old man with recurrent basal cell carcinoma of the left medial canthus. Top, Thickening of the left lower eyelid and medial ectropion. Middle, Appearance after Mohs' excision. Bottom, Appearance seven years after exenteration.

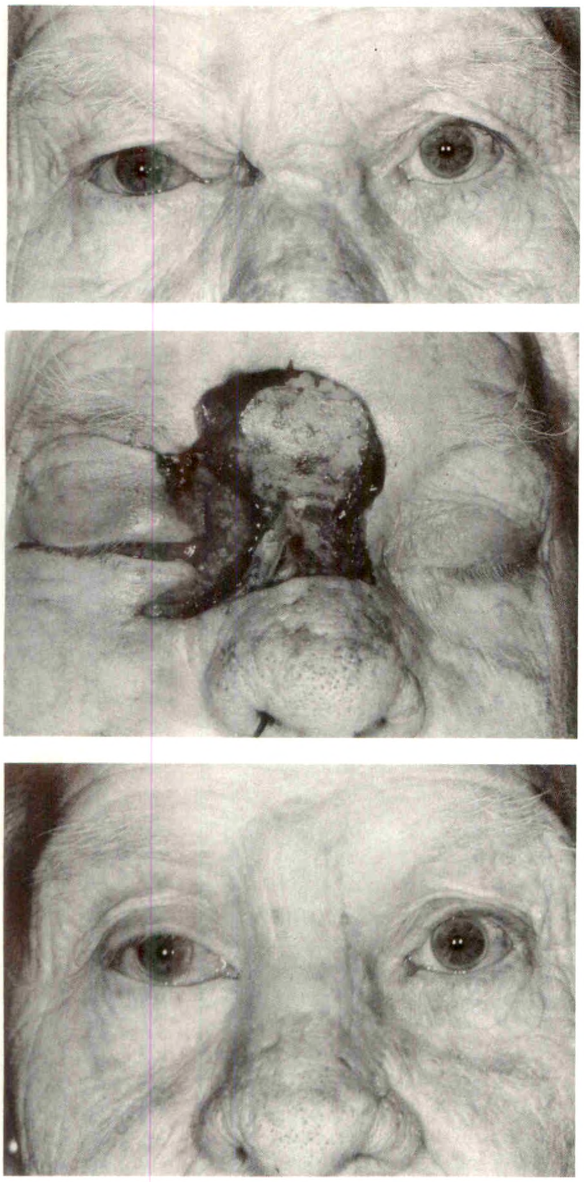

Fig. 2 (Howard and associates). Case 2. A 78-year-old woman with recurrent basal cell carcinoma of the right medial canthus. Top, Ulcerated mass attached to underlying bone. Middle, Appearance after Mohs' excision. Bottom, Appearance four years after reconstruction with median forehead flap.

nance imaging scans performed seven months postoperatively showed no tumor progression. No clinical signs of tumor recurrence were observed externally (Fig. 3, top right).

Case 4

A 75-year-old white man was referred to our institution in 1988. He had received radiotherapy for acne at the age of 18 years. Since the age of 40 years he had multiple skin cancers removed from the face. On examination he had a 0.8 × 0.3-cm ulcerating tumor on the left lateral canthal skin that had been enlarging progressively for four years and an incomitant strabismus (Fig. 4, top). A computed tomographic scan showed a soft-tissue mass with lacrimal gland and scleral involvement (Fig. 4, bottom). No bone erosion was noted. Basal cell carcinoma was confirmed by biopsy. An exenteration was recommended. The patient refused. The patient subsequently received 6,000 cGy of radiation to the affected area. The extraocular motility returned to normal with marked reduction of the lateral canthal ulcer. Three years later the ulcer and subconjunctival eyelid mass returned.

Results

Orbital invasion of cutaneous basal cell and squamous cell carcinoma was documented in 13 patients (2.5% of all basal cell or squamous cell eyelid tumors) seen during a six-year period. Nine of these patients underwent orbital exenteration. The four remaining patients refused exenteration. Three patients in the latter group received radiotherapy and one was treated with surgical excision without free margins with cryotherapy applied to the orbital fat and orbital bones.

The average age of the patients at initial diagnosis of a basal cell cancer was 59.5 years (range, 36 to 82 years). The average age at exenteration was 75.7 years (range, 54 to 92 years). The two patients with squamous cell carcinoma were 71 years and 79 years old at development of the initial lesion and underwent exenteration for orbital invasion one year later. Eight men and three women had invasive basal cell carcinoma. Both patients with squamous cell carcinoma were men.

All patients in our series had an indurated or ulcerated eyelid mass at initial examination. Incomitant strabismus was seen in ten patients at our initial examination. Progressive ocular motility restriction developed over a period of months to years. Despite obvious clinical signs of epiphora and exposure keratopathy in several patients, symptomatic complaints were not usually volunteered. Nine patients had recurrent lesions; two patients had radiotherapy to the face and the remaining two patients had large neglected tumors (greater than 2.5 cm) at initial examination.

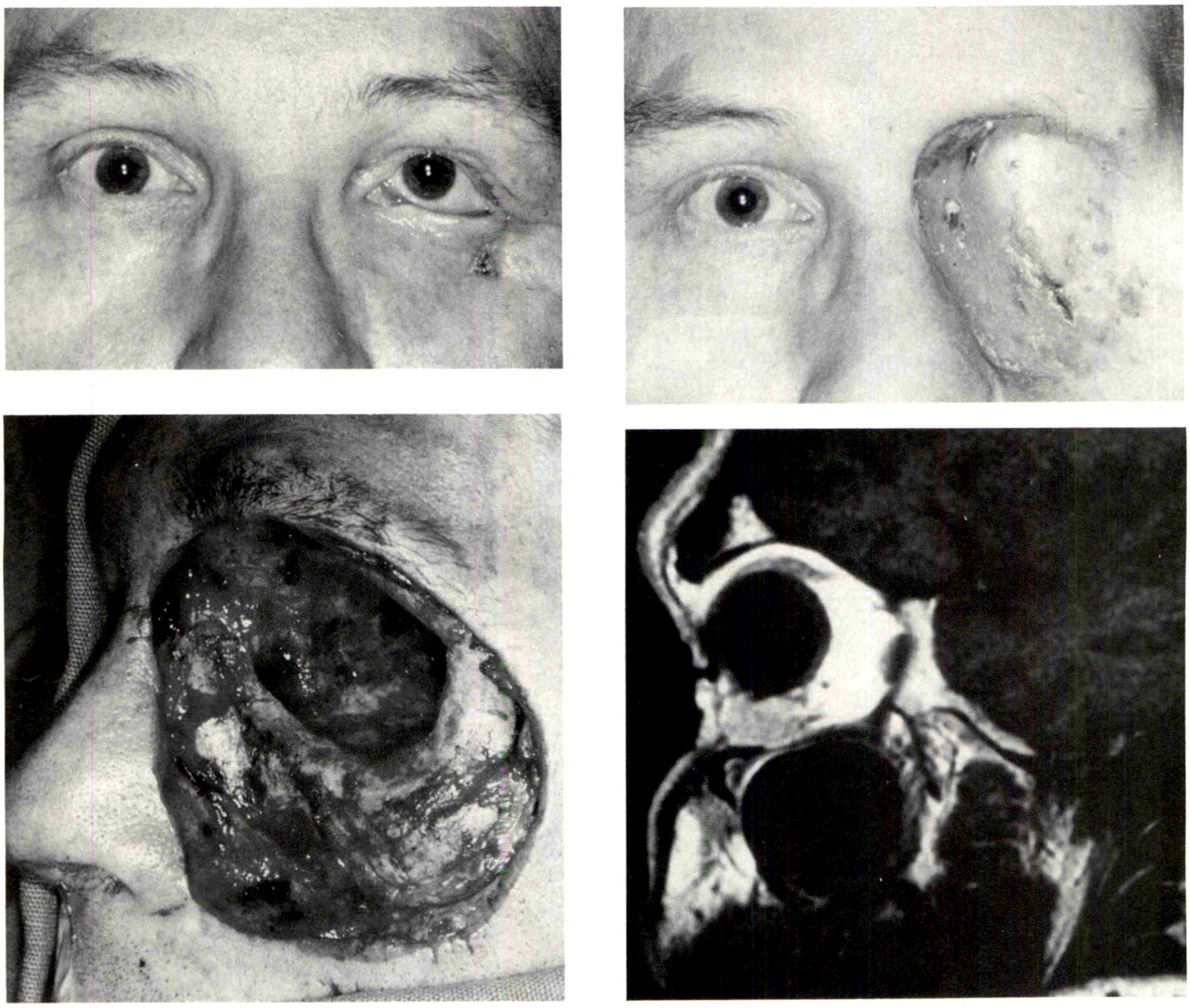

Fig. 3 (Howard and associates). Case 3. A 54-year-old man with recurrent basal cell carcinoma of the left lower eyelid. Top left, Left lower eyelid ectropion, with ulcerated mass adherent to underlying bone. Top right, Appearance seven months after radical exenteration. Bottom left, Intraoperative photograph showing exenteration and area of Mohs' excision. Lateral and inferior rims were removed subsequently. Bottom right, Magnetic resonance imaging scan showing involvement of inferior rectus muscle and globe.

An orbital mass was most commonly located in the lower eyelid. Four lesions were exclusively located in the lower eyelid. One lesion was found in the lower eyelid with extension into the medial canthal region. Similarly, one lesion was in both the lower eyelid and lateral canthal region. Three lesions were found in the medial canthal and three were found in the lateral canthal area. Only one lesion was found in the upper and lateral eyelid.

The mean duration from initial diagnosis of a cutaneous basal cell carcinoma to a diagnosis of orbital invasion was 9.8 years (range, one to 18 years). Orbital invasion from cutaneous squamous cell carcinoma appeared to develop at a more rapid rate. Both cases of squamous cell invasion developed within one year of initial diagnosis of tumor.

Excision or treatment of the cutaneous eyelid tumors was previously attempted in ten patients. Multiple excisions were required in eight patients. Carcinomas progressed to invasion in three patients before medical care was sought. Additional treatment approaches used in our patients included excision and follow-up radiotherapy in three patients; and excision, cryotherapy, and radiotherapy in one patient.

Five patients had been exposed to radiation before exenteration. Two patients received facial radiotherapy for acne during their youth.

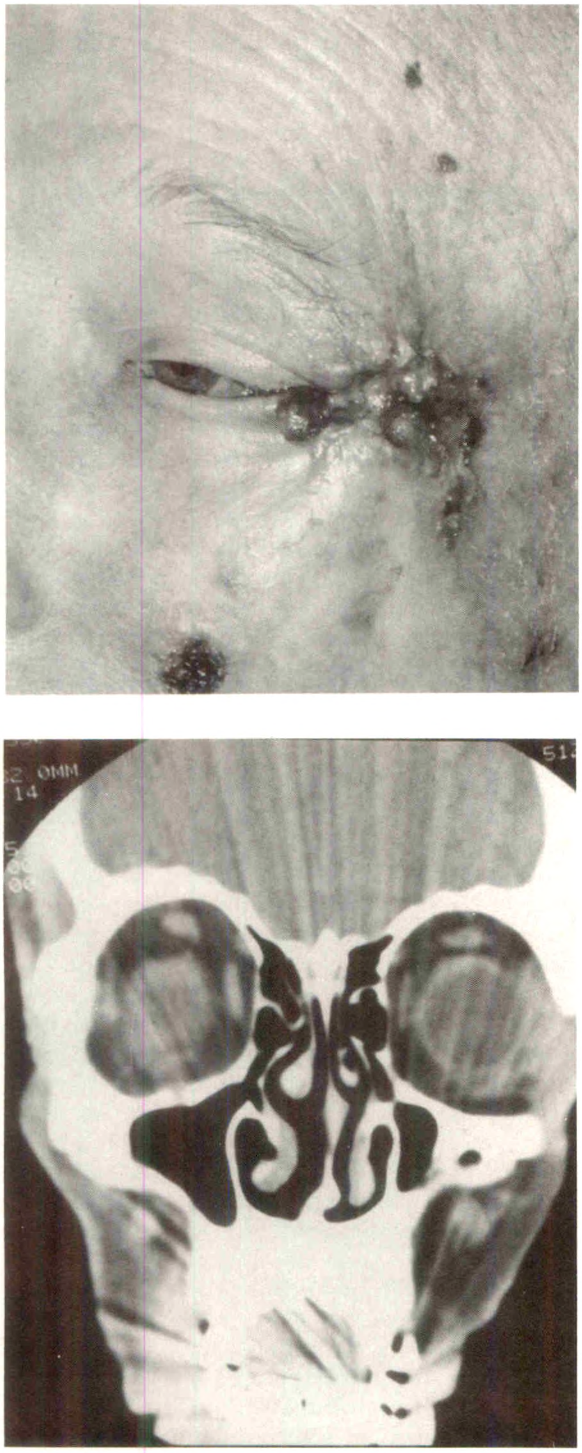

Fig. 4 (Howard and associates). Case 4. A 75-year-old white man with recurrent basal cell carcinoma of the left lateral canthus. Top, Wide area of ulceration pulling eyelids temporally. Bottom, Computed tomographic scan showing involvement of lateral rectus muscle, eye, and lacrimal gland. Apparent absence of bone was thought to be caused by asymmetry from rotation.

Three patients received 5,400 to 5,900 cGy as part of a treatment regimen for recurrent basal cell carcinoma before our examination.

Radiologic studies were performed on all patients. Ten patients were examined with orbital computed tomography and the remaining three patients were examined with magnetic resonance imaging. All of the scans showed an orbital soft-tissue mass. Bone erosion was noted in five patients. Two patients with bone erosion had unresectable tumors.

Preoperative and postoperative Mohs' microsurgical measurements were made in 11 patients. The average initial lesion before an operation measured 2.1 cm^2 (range, 0.12 to 12.0 cm^2). Postoperatively, the average defect size was 25.7 cm^2 (range, 3.0 to 75.0 cm^2). The average increase in size of the Mohs' microsurgical defect was 12.3 times the size of the initial lesion.

A histologic review of our 13 cases disclosed one nodular common basal cell carcinoma, eight morphea-sclerosing basal cell carcinomas, two basosquamous cell carcinomas, and two squamous cell carcinomas. Four of the nine patients who had undergone exenteration had tumors demonstrating neurotropy not identified by biopsy.

Nine exenteration specimens were obtained. The margins of resection were free of tumor in seven specimens. One patient had extension of the tumor into the trigeminal ganglion noted during a second operative procedure. The second patient had tumor extension into the superior orbital fissure and adjacent dural tissue. All exenteration specimens confirmed the tumor type found on the initial incisional biopsy.

The longest patient follow-up was seven years in two patients. The average follow-up was 2.7 years. One patient who refused exenteration and radiotherapy died two years after diagnosis from causes unrelated to the orbital invasion. Another patient with squamous cell carcinoma died from causes unrelated to his orbital tumor one year after exenteration. Recurrence of tumor has not been documented in any patient who underwent exenteration, although the follow-up period in many of these patients was too short to suggest a cure resulted.

Discussion

Orbital invasion from cutaneous basal cell and squamous cell carcinoma does not usually develop. In our study, orbital exenteration was performed in nine of 622 eyelid tumors (1.4%, basal and squamous cell carcinoma). Payne and associates[1] reported exenteration of 3.6% of 273 eyelid basal cell lesions. In a similar study, Perlman and Hornblass[2] found four of 106 patients with basal cell lesions requiring exenteration. Invasion of the orbit by basal cell carcinoma and squamous cell carcinoma was documented in 2.4% and 8.2%, respectively, of 764 consecutive orbital tumors seen at the Mayo Clinic.[3] In 504 expanding lesions of the orbit reported by Reese,[4] only 0.8% were basal cell and 0.2% were squamous cell lesions from the eyelid. Shields and associates[5] found basal cell tumors accounted for 3% and squamous cell carcinoma accounted for less than 1% of all orbital space-occupying lesions in a series of 645 patients at the Wills Eye Hospital. These studies demonstrate the relative infrequency of orbital invasion of cutaneous carcinomas, but do not describe specific patient characteristics.

In our study, the average age at diagnosis of invasion (75.8 years) and gender distribution (ten men and three women) of our patients was consistent with age-related case reports of exenteration for basal cell carcinoma.[2,6,7-9] Case reports of basal cell carcinoma without orbital invasion show either gender predilection or a male to female ratio that approximates 2 to 1.[1,2,10-17] The consistent male predominance, however, found in our cases and other cases of exenteration for invasive basal cell and squamous cell carcinoma[7-9] suggests that men are at greater risk than women for orbital invasion.

An indurated palpable periocular mass or ulcerated lesion was the most frequent finding at initial examination and was found in all patients in our study. Ocular motility disturbances were found in ten of our 13 patients (76.9%). Several patients had severe restriction of eye movement in all quadrants. Simons, Robinson, and Masters[7] reported a relatively painless mass as the most common symptom in their study of malignant tumors of the orbit treated by exenteration. This was supported by Payne and associates,[1] who found symptoms of a mass or growth, irritation, ulceration, and bleeding accounted for the majority of basal cell tumors of the eyelid. Callahan, Wilkins, and Dowling's study[14] involved 11 cases of massive orbital invasion by small malignant lesions, of which ten were basal cell and one was squamous cell in origin. Four of the patients with basal cell tumors in their study had ocular motility disturbances. An orbital mass often accompanied by diplopia appears to be the most common finding at initial identification of orbital invasion.

Our observation of the lower eyelid as the most common initial site of cutaneous basal cell carcinoma confirms previous reports.[1,11] Only one lesion in our study was not found on the lower eyelid or canthi. The association between medial canthal basal cell carcinoma and an increased risk of orbital invasion and death has been emphasized by several authors.[11,15,16] We did not find a correlation regarding medial canthal location, invasion, or death. Medial and lateral canthal locations were evenly distributed among patients. Furthermore, there was no clear indication that treatment of medial canthal lesions or delay in diagnosis of orbital invasion differed from those in the lateral canthal region. Our data did not support Mohs'[17] statement that medial canthal basal cell lesions are more invasive and spread more commonly along the periosteum than lesions originating from other periocular regions. Additionally, we could not substantiate Aurora and Blodi's[11] statement that medial canthal basal cell lesions are 1.5 times larger or more extensive than those in the lower eyelid.

Orbital invasion from basal cell carcinoma developed over an average period of ten years. No difference in the duration of disease was noted between patients who underwent repeated excision and those who did not seek any previous medical treatment of cutaneous lesions. Rathbun, Beard, and Quickert[18] reported 14 exenteration cases for similar lesions with a delay of 8.5 years. The duration seen in isolated case reports is ten years or longer.[19-21] Invasive orbital disease resulting from cutaneous squamous cell carcinoma develops much earlier than disease resulting from basal cell lesions. Both cases in our series developed over one year. Two of three cases of invasive squamous cell carcinoma seen by Rathbun, Beard, and Quickert[18] developed within three years of initial cutaneous diagnosis.

Three patients in our series had large untreated lesions for ten or more years. Denial of existing medical problems is unfortunately well known. Continued efforts at public education regarding the benefits of early diagnosis and treatment are the answer to the problem. Perhaps more alarming is that the remaining nine patients had at least one previous treatment attempt. One patient (Case 3) underwent more than 20 operations in a 17-year period. Both patients with intracranial spread were under continued treatment (excisions for Case 3 and radiotherapy for Case 13) while intracranial disease developed. An earlier diagnosis and treatment of orbital invasion might have prevented deeper involvement.

It is well documented in the literature that periocular tumors frequently extend well beyond the obvious clinical margin.[22,23] Careful pathologic examination of the surgical margins must be made at the time of excision. If any question exists, further excision must be performed. Surgeons should not reconstruct an area with positive margins and depend on the immunologic system to cure the microscopic disease. At our institution a large part of our practice is the joint management of positive margin excisions or recurrent tumors of the eyelid and canthi. Yet we are often surprised at the size of the resultant defect after excision of morphea or recurrent tumors. We believe separating the excising surgeon from the reconstructing surgeon as in Mohs' microsurgery decreases the possibility of recurrent tumor.

Various surgical techniques used in early management of these lesions outside our institution have complicated the analysis of whether tumors recurred because of their aggressive course or because of repeated inadequate treatment. In many cases, we have incomplete data on the margins of resection for the early cutaneous lesions and cannot comment on this point.

Similarly, we cannot comment on the role that radiation may have had in the aggressive course of these tumors. It is well known that facial radiotherapy for acne (two of our patients) contributes to the development of basal cell carcinoma, but there are many similar patients who do not develop orbital invasion. Similarly, the three patients who underwent radiotherapy for their recognized recurrence may have had initial aggressive tumors. In one case in which the patient refused exenteration and radiation was used, the initial response was quite impressive with most of the ulceration resolving rapidly. Unfortunately, massive orbital involvement appeared within two years. As previously suggested, inadequate excision or radiotherapy may delay more aggressive intervention that may result in cure.

Orbital invasion was detected preoperatively on all patients using magnetic resonance imaging or computed tomography. The use of computed tomography in detecting these tumors is well documented.[20,21,24] The typical appearance is an orbital soft-tissue density mass located in the area of the cutaneous process. Bony erosion was noted in four of the computed tomographic scans and on one magnetic resonance imaging scan. Because a magnetic resonance imaging scan will not show bone detail, bony erosion is recognized in areas where soft-tissue signals replace the linear lack of signal from the normal orbital bones. The tumor, shown on magnetic resonance imaging, extended from the orbit into the maxillary sinus. The bony erosion was confirmed at the time of the operation. The finding of bony erosion may have been an indication of an aggressive tumor in these particular cases, because two of these patients had unresectable tumors.

The morphea subtype of basal cell carcinoma often causes subclinical extension; consequently, appropriate clinical resection margins are difficult to determine. This pattern is infiltrative and has the capacity to invade deeply into orbital tissues.[25] The preferential tendency of tumor cells to infiltrate along nerves in some cases is an ominous sign suggesting probable invasion into orbit and skull. Recurrent basal cell carcinoma confirmed by biopsy often has a mixture of scar tissue and basaloid cells, thereby making pathologic identification of margins difficult. The average post-Mohs' microsurgical skin defect was 12.3 times the presurgical clinical dimensions, thereby demonstrating the difficulty in defining tumor margins on a clinical basis. This is not surprising given the morphea characteristics of these tumors at the time of orbital invasion.

Surgical excision of the tumor with an orbital exenteration was recommended to all 13 patients. Nine patients underwent standard exenteration with coverage by a split-thickness skin graft. Two of these patients had unresectable tumors. Four patients refused the operation partly on the basis of their fear of facial disfigurement and hospitalization. One patient underwent Mohs' microsurgery, but refused exenteration and was treated with deep orbital resection, liquid nitrogen cryotherapy, and myocutaneous advancement flap closure. Two others received orbital radiation and one refused all modalities of treatment.

Our longest follow-up has been in the patients with basal cell carcinoma. Eight patients have been monitored for more than two years. One patient died one year after our examination from an unrelated, and previously undiagnosed, lung cancer. Interestingly, she was the one patient who refused exenteration and radiotherapy. Both patients with squamous cell carcinoma were monitored for one year. One of these patients had an unresectable lesion with intracranial extension, but died of unrelated causes. The second patient has had no evidence of recurrence since the exenteration. Recurrence had not been detected in any patient who underwent exenteration. It must be emphasized that the two-year follow-up cannot determine whether the patients were cured. In these patients, a five- to ten-year follow-up without recurrence of tumor would only be considered minimal in regard to cure.

The diagnosis of orbital invasion should not be missed clinically. Orbital invasion should be suspected in patients with skin cancer who have an indurated orbital mass and diplopia at initial examination. Most often these patients are men who are 60 to 70 years of age. Usually, these patients have not ignored their disease, but have often undergone multiple attempts at cure. These patients may feel that they have been well cared for and are not at risk for serious sequelae. Similarly, the extended course of the tumor may give the patient (and the doctor) a false sense of security. The true peripheral extent of the tumor is often not obvious clinically because of the morphea characteristics. These aggressive tumors do not necessarily originate medially as suggested by others. Previous radiotherapy for treatment of the initial tumor or a recurrence should be warnings of potential invasion.

With appreciation of the aggressive course of cutaneous carcinomas in patients with these clinical characteristics, physicians may be able to prevent orbital invasion. Patients with large previously untreated tumors or recurrent tumors of any size in the periocular area must be treated aggressively in the early stages of disease to prevent orbital invasion and subsequent loss of vision, deformity, and intracranial spread.

References

1. Payne, J. W., Duke, J. R., Butner, R., and Eifrig, D. E.: Basal cell carcinoma of the eyelids. A long-term follow-up study. Arch. Ophthalmol. 81:553, 1969.

2. Perlman, G. S., and Hornblass, A.: Basal cell carcinoma of the eyelids. A review of patients treated by surgical excision. Ophthalmic Surg. 7:23, 1976.

3. Henderson, J., and Farrow, G. M.: The tumor survey. In Orbital Tumors, ed. 2. New York, Thieme Stratton, 1980, pp. 67–74.

4. Reese, A. B.: Expanding lesions of the orbit. Trans. Ophthalmol. Soc. U.K. 91:85, 1971.

5. Shields, J. A., Bakewell, B., Augsburger, J. J., and Flanagan, J. C.: Classification and incidence of space-occupying lesions of the orbit. A survey of 645 biopsies. Arch. Ophthalmol. 102:1606, 1984.

6. Lo, J. S., Snow, S. N., Reizner, G. T., Mohs, F. E., Larson, P. O., and Hruza, G. J.: Metastatic basal cell carcinoma. Report of twelve cases with a review of the literature. J. Am. Acad. Dermatol. 24:715, 1991.

7. Simons, J. N., Robinson, D. W., and Masters, F. W.: Malignant tumors of the orbit and periorbital structures treated by exenteration. Plast. Reconstr. Surg. 37:100, 1966.

8. Savage, R. C.: Orbital exenteration and reconstruction for massive basal cell and squamous cell carcinoma of cutaneous origin. Ann. Plast. Surg. 10:458, 1983.

9. Naquin, H. A.: Exenteration of the orbit. Arch. Ophthalmol. 51:850, 1954.

10. Einauglar, R. B., and Henkind, P.: Basal cell epithelioma of the eyelid. Apparent incomplete removal. Am. J. Ophthalmol. 67:413, 1969.

11. Aurora, A. L., and Blodi, F. C.: Reappraisal of basal cell carcinoma of the eyelids. Am. J. Ophthalmol. 70:329, 1970.

12. Hollander, L., and Krugh, F. J.: Cancer of the eyelid. Am. J. Ophthalmol. 29:244, 1944.

13. Cobb, G. M., Thompson, G. A., and Allt, W. E. C.: Treatment of basal cell carcinoma of the eyelids by radiotherapy. Can. Med. Assoc. J. 91:743, 1964.

14. Callahan, A., Wilkins, R. B., and Dowling, E. A.: Massive orbital invasion by small malignant lesions. South. Med. J. 68:271, 1975.

15. Wiggs, E. O.: Basal cell carcinoma of the medial canthus. Its orbital implications. Mod. Probl. Ophthalmol. 14:549, 1975.

16. Charles, N. C.: Basal cell carcinomas of the eyelids. Pitfalls in diagnosis and therapy. J. Dermatol. Surg. 1:28, 1975.

17. Mohs, F. E.: The chemosurgical method for the microscopically controlled excision of radioresistant facial cancer. Am. J. Roentgenol. Radium Ther. Nucl. Med. 73:61, 1955.

18. Rathbun, J. E., Beard, C., and Quickert, M. H.: Evaluation of 48 cases of orbital exenteration. Am. J. Ophthalmol. 72:191, 1971.

19. Weimar, V. M., and Ceilley, R. I.: Basal cell carcinoma of a medial canthus with invasion of supraorbital and supratrochlear nerves. Report of a case treated by Mohs' technique. J. Dermatol. Surg. Oncol. 5:279, 1979.

20. Hornblass, A., and Roen, J. L.: A combined facial, orbital and intracranial resection of extensive basal cell carcinoma arising in the eyelid. Ophthalmic Surg. 16:769, 1985.

21. Tomich, J. M., and Wagner, R. F.: Late recurrent basal cell carcinoma presenting as a unilateral exophthalmos. J. Dermatol. Surg. Oncol. 12:866, 1986.

22. Ceilley, R. I., and Anderson, R. L.: Microscopically controlled excision of malignant neoplasms on and around eyelids followed by immediate surgical reconstruction. J. Dermatol. Surg. Oncol. 4:44, 1978.

23. Nerad, J. A., and Whitaker, D. C.: Periocular basal cell carcinoma in adults 35 years of age and younger. Am. J. Ophthalmol. 106:723, 1988.

24. Clouston, P. D., Sharpe, D. M., Corbett, A. J., Kos, S., and Kennedy, P. J.: Perineural spread of cutaneous head and neck cancer. Its orbital and central neurological complications. Arch. Neurol. 47:73, 1990.

25. Lever, W. F., and Schaumberg-Lever, G.: Histopathology of the Skin. Philadelphia, J. B. Lippincott, 1983, pp. 562–575.

OPHTHALMIC MINIATURE

"Voilà! pour vous," said he, drawing his hand from his waistcoat, and placing on my desk a letter—the very letter I had seen in Rosine's hand—the letter whose face of enamelled white and single Cyclop's eye of vermilion red had printed themselves so clear and perfect on the retina of an inward vision. I knew it, I felt it to the letter of my hope, the fruition of my wish, the release from doubt, the ransom from my terror.

Charlotte Brontë, *Villette*
Oxford, England, Oxford University Press, 1978, p. 237

The Prognostic Value of Preoperative Dacryocystography in Endoscopic Intranasal Dacryocystorhinostomy

Geva E. Mannor, M.D., and Arthur L. Millman, M.D.

Endoscopic intranasal dacryocystorhinostomy has been used as a primary treatment of lacrimal obstruction and for revision of conventional dacryocystorhinostomy. This study correlates dacryocystographic anatomy with the success of the endoscopic surgical technique. Eighteen patients with epiphora and nasolacrimal obstruction underwent operations. Preoperative dacryocystography identified 11 patients with either normal or enlarged lacrimal sacs, and seven patients with cicatrized lacrimal sacs. Patients with lacrimal sac stones and tumors were excluded. Endoscopic intranasal dacryocystorhinostomy was successful in nine of 11 (82%) patients with normal or enlarged lacrimal sacs, and in two of seven (29%) patients with cicatrized lacrimal sacs. The endoscopic technique was much more successful with normal or enlarged lacrimal sacs than with cicatrized lacrimal sacs (P = .049). Lacrimal sac anatomy as determined by preoperative dacryocystography is an important prognostic factor in technically achieving surgical success.

ENDOSCOPIC INTRANASAL dacryocystorhinostomy has been used as a primary treatment of lacrimal obstruction and for the revision of conventional dacryocystorhinostomy.[1-4] This technique allows direct visualization, evaluation, and treatment of the intranasal abnormalities that can cause surgical failure. Additionally, the endoscopic technique obviates a skin incision. Lacrimal sac anatomy and abnormalities and their relationship to surgical success have not been well studied. This study correlates preoperative dacryocystography and lacrimal sac anatomy with surgical outcome in endoscopic intranasal dacryocystorhinostomy.

Subjects and Methods

Between September 1989 and April 1990, 18 patients with epiphora underwent endoscopic intranasal dacryocystorhinostomy performed by one of us (A.L.M.). All patients underwent complete preoperative ophthalmic examinations. Nasolacrimal obstruction was documented by Jones I and Jones II dye tests, Schirmer basic tests, lacrimal probing and irrigation, and nasal speculum examination. Ten of the 18 patients had undergone a previous conventional dacryocystorhinostomy, whereas eight patients had not undergone previous nasolacrimal operations. Patients ranged in age from 18 to 72 years; 12 were women and six were men. No other ophthalmic abnormality was observed in these patients. All patients underwent standard preoperative dacryocystography.[5,6] Dacryocystography classified lacrimal sacs by size into the following two groups: normal or enlarged (in 11 patients), and cicatrized (in seven patients; Figs. 1 and 2).

The operation was performed with the patient under general endotracheal anesthesia after packing the nose with 1:100,000 epinephrine and 4% cocaine. Endoscopic intranasal dacryocystorhinostomy was performed by one of us (A.L.M.) via a rigid endoscope with either a 0- or a 30-degree viewing angle.[3-5]

After a nasal mucosal flap was lifted, a 23-gauge retinal light pipe was placed via the punctum and canaliculus into the lacrimal sac. The location of the bone to be removed was identified endoscopically by transillumination of the light pipe through the lacrimal sac wall, bone, and nasal mucosa.[4] Mucosa and any scar tissue were lifted with a sickle knife. Bone was removed with a 30-degree or back-biting rongeur. Otologic alligator forceps and scissors

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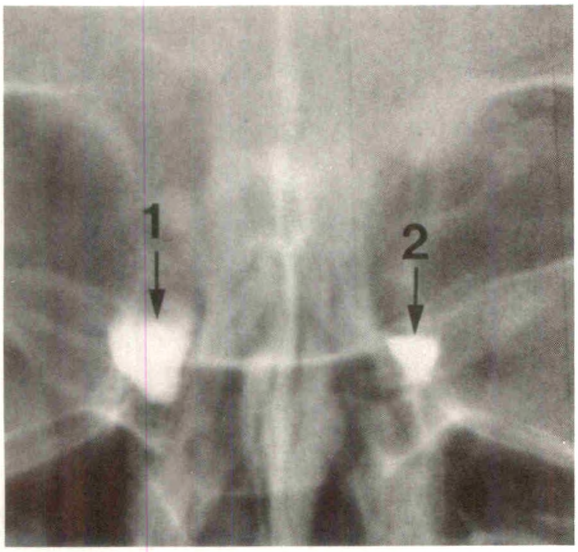

Fig. 1 (Mannor and Millman). Preoperative dacryocystogram demonstrating radiopaque dye filling a 4+ enlarged lacrimal sac (arrow 1) and a 2+ enlarged lacrimal sac (arrow 2). Sac enlargement was judged on a scale of 1+ to 4+, with 1+ being minimal and 4+ being maximal. Note the fluid level of the dye in both sacs.

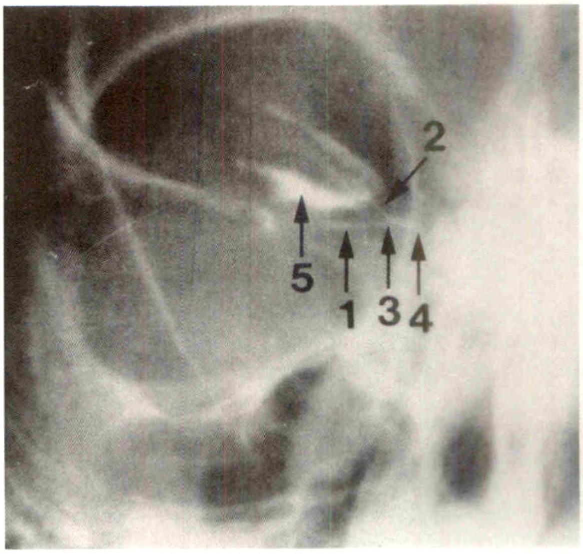

Fig. 2 (Mannor and Millman). Preoperative dacryocystogram demonstrating radiopaque dye injected via the lower canaliculus (arrow 1) with retrograde filling of the upper canaliculus (arrow 2) and filling of the common canaliculus (arrow 3). Despite patency of the canalicular system, lack of dye distal to arrow 4 indicates that the lacrimal sac is completely cicatrized and cannot fill with dye. Arrow 4 denotes the location of a small, scarred lacrimal sac; compare with lacrimal sac filled with dye in Figure 1 (arrow 2). Note the reflux of dye into the conjunctival fornices (arrow 5).

incised the lacrimal sac. An intranasal ostium of at least 15 mm in diameter was achieved. The canaliculi were intubated with Silastic tubing that allowed for tenting of the lacrimal sac and of residual nasal mucosa, and sutureless mechanical apposition between lacrimal sac and nasal mucosa flaps. The Silastic tubing was left in place for three months.

Statistical analysis involved the use of Fisher's exact *t*-test to calculate two-tailed P values for surgical success vs failure (Statistical Analysis Software, SAS Institute, Inc., Cary, North Carolina).

Results

In the ten patients who underwent revision of previous nasolacrimal procedures, intraoperative findings included scarring and closure of the intranasal lacrimal drainage ostia in seven patients, and turbinate or septal synechiae in five patients. Two patients had scarring of the ostia and turbinate or septal synechiae.

No intraoperative or postoperative complications were observed. Follow-up ranged from 12 to 19 months. An operation was defined as a success if preoperative epiphora resolved and nasolacrimal patency was confirmed by lacrimal irrigation. Of the eight patients undergoing primary operations, five had normal or enlarged lacrimal sacs and three had cicatrized lacrimal sacs as determined by preoperative dacryocystography. Primary endoscopic operations were successful in four of five (80%) patients with normal or enlarged lacrimal sacs and in one of three (33%) patients with cicatrized lacrimal sacs. Of the ten patients undergoing revision of previous standard (external) dacryocystorhinostomy, six had normal or enlarged lacrimal sacs and four had cicatrized lacrimal sacs as determined by preoperative dacryocystography. Revisional endoscopic operations were successful in five of six (83%) patients with normal or enlarged lacrimal sacs and in one of four (25%) patients with cicatrized lacrimal sacs. By combining primary and secondary (revisional) operations, statistically significant results were obtained. Endoscopic intranasal dacryocystorhinostomy was successful in nine of 11 (82%) patients with normal or enlarged lacrimal sacs but only in two of seven

(29%) patients with cicatrized lacrimal sacs (P = .049). Patient age, gender, and type of operation (primary vs revisional) did not have a statistically significant effect on surgical outcome.

Discussion

Dacryocystorhinostomy has traditionally been performed via a skin incision or via a transethmoidal route in an attempt to make an anastomosis between the lacrimal sac and the nasal mucosa.[7] The size of this surgical anastomosis does not correlate with surgical success.[8] Some authors believe the average diameter of the intranasal ostium shrinks postoperatively to 2% of the original operative diameter.[9] Scarring of the ostium and errors in ostium location are the major causes of surgical failure.[10,11] Because it allows direct intranasal visualization, the endoscopic approach avoids these common causes of surgical failure.

To compare surgical outcome across a uniformly consistent surgical technique and assure a clinically correct analysis, we limited our study to those patients operated on by us. Thus, we did not enroll additional patients who were operated on by other surgeons who might have used different endoscopic surgical techniques. Although this limited the number of surgical cases in our study, our results were nonetheless statistically significant (P = .049).

Our study suggests that with lacrimal sac cicatrization, as develops in chronic dacryocystitis, the endoscopic intranasal technique has distinctly limited success. Surgical success requires that the lacrimal sac and nasal mucosal flaps be meticulously apposed to ensure adequate fistulization and nasolacrimal patency. Lacrimal sac abnormalities have been implicated as an important cause of dacryocystorhinostomy failure, with one study reporting sac abnormalities in 43 of 209 surgical failures.[10] Unfortunately, with a cicatrized lacrimal sac in which a minimal amount of lacrimal mucosa is available, the endoscopic intranasal technique makes it technically difficult to fashion and manipulate these delicate flaps.

Thus, when considering endoscopic intranasal dacryocystorhinostomy, preoperative dacryocystography may provide important prognostic information concerning the success of the planned surgical procedure. This imaging study should ensure enough lacrimal sac mucosa for adequate mucosal flap manipulation and exclude lacrimal sac abnormalities, such as cicatrization, lacrimal sac stones, and tumors. When preoperative dacryocystography discloses a cicatrized lacrimal sac, a conventional dacryocystorhinostomy via the external skin approach may provide the additional necessary exposure for mucosal flap manipulation. In these difficult cases, careful microscopic canalicular anastomosis via a canaliculodacryocystorhinostomy may be indicated.[12]

We believe that endoscopic intranasal dacryocystorhinostomy is a new technique in evolution. Its usefulness may be limited, however, to specific anatomic and radiographic indications. We are currently using video-directed laser-assisted modalities including potassium titanyl phosphate-YAG and holmium-YAG lasers. Analysis of lacrimal sac anatomy and abnormalities via preoperative dacryocystography will allow future comparison of the efficacy of standard and endoscopic techniques.

We believe that with a 95% success rate, conventional external dacryocystorhinostomy still has the highest rate of success.[8] However, the near future will demonstrate notable progress in endoscopic intranasal dacryocystorhinostomy.

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References

1. McDonogh, M., and Meiring, J. H.: Endoscopic transnasal dacryocystorhinostomy. J. Laryngol. Otol. 103:585, 1989.
2. Rice, D. H.: Endoscopic intranasal dacryocystorhinostomy results in four patients. Arch. Otolaryngol. Head Neck Surg. 116:1061, 1990.
3. Metson, R.: The endoscopic approach for revision dacryocystorhinostomy. Laryngoscope 100:1344, 1990.
4. Massaro, B. M., Gonnering, R. S., and Harris, G. J.: Endonasal laser dacryocystorhinostomy. A new approach to nasolacrimal duct obstruction. Arch. Ophthalmol. 108:1172, 1990.
5. Hurwitz, J. J., and Victor, W. H.: The role of sophisticated radiological testing in the assessment and management of epiphora. Ophthalmology 92:407, 1985.

6. Millman, A. L., Liebskind, A., and Putterman, A. M.: Dacryocystography. The technique and its role in the practice of ophthalmology. Radiol. Clin. North Am. 25:781, 1987.

7. Patrinely, J. R., and Anderson, R. L.: A review of lacrimal drainage surgery. Ophthalmic Plast. Reconstr. Surg. 2:97, 1986.

8. Bumsted, R. M., Linberg, J. V., Anderson, R. L., and Barreras, R.: External dacryocystorhinostomy. A prospective study comparing the size of the operative and healed ostium. Arch. Otolaryngol. 108:407, 1982.

9. Linberg, J. V., Anderson, R. L., Bumsted, R. M., and Barreras, R.: Study of intranasal ostium external dacryocystorhinostomy. Arch. Ophthalmol. 100:1758, 1982.

10. Welham, R. A., and Wulc, A. E.: Management of unsuccessful lacrimal surgery. Br. J. Ophthalmol. 71:152, 1987.

11. Allen, K. M., Berlin, J., and Levine, H. L.: Intranasal endoscopic analysis of dacryocystorhinostomy failure. Ophthalmic Plast. Reconstr. Surg. 4:143, 1988.

12. Doucet, T. W., and Hurwitz, J. J.: Canaliculodacryocystorhinostomy in the management of unsuccessful lacrimal surgery. Arch. Ophthalmol. 100:619, 1982.

Incidence of Enucleation in a Defined Population

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We conducted a population-based study of long-term trends in the incidence of enucleation. From 1956 through 1988, enucleation was performed on 99 residents (55 males and 44 females) of Olmsted County, Minnesota. The mean annual age-adjusted incidence per 100,000 population for males (5.17) was 50% greater than that for females (3.49; P = .04). An increase in the enucleation rate was noted with increasing age (P = .001), with the highest incidence in patients who were 70 to 79 years of age. A decrease in the incidence of enucleation over time (P = .002) was observed in Olmsted County residents who were at least 40 years of age and was caused primarily by the decreasing incidence of neovascular glaucoma and tumor-related enucleations. The incidence of traumatic enucleations did not significantly decrease (P = .25) over this three-decade study period.

ENUCLEATION is an acceptable therapeutic modality for severely traumatized eyes, certain intraocular tumors, and blind painful or cosmetically unacceptable eyes. Little data exist, however, concerning the incidence of enucleation in a defined population in the United States. Most surveys on the causes of enucleation have been limited to tertiary care centers or eye hospitals that receive referrals from large geographic areas.[1-5] Clinical and demographic characteristics of patients who are referred to major medical centers frequently differ from characteristics of those patients who are treated in their own community. As a result, the distribution of eye conditions leading to enucleation in community hospitals may be different from those seen in trauma or academic medical centers.[6]

The primary purposes of this study were to determine the incidence of enucleation in a defined population and to assess trends in the types of conditions that led to enucleation in the 33-year period from 1956 through 1988 in the population of Olmsted County, Minnesota. These incidence data have been considered in light of time trends in the management of predisposing factors for enucleation.

Material and Methods

Study setting—Population-based epidemiologic research is possible in Rochester, Minnesota, because medical care is largely self-contained within the community and is delivered by a few providers. Most ophthalmic care for residents of this community is provided by the Mayo Clinic, which has maintained a common medical and surgical record with its two large affiliated hospitals for the past 80 years. The diagnoses and surgical procedures of essentially all Olmsted County residents are indexed, and the original medical records can easily be retrieved for review.[7] The Rochester Epidemiology Project maintains a similar index of diagnoses and surgical procedures recorded by other institutions serving Olmsted County, including the Olmsted Medical Group, the Olmsted Community Hospital, Rochester State Hospital, the Veterans' Administration and University of Minnesota Hospitals in Minneapolis, and other hospitals and practitioners in the vicinity. These indexes incorporate the diagnosis given to outpatients seen in office or clinical consultations, emergency room visits, house calls, and nursing home visits, as well as the diagnoses

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recorded for hospital inpatients, on death certificates, and at autopsy. The usefulness of this data retrieval system for population-based studies was described previously.[7,8]

Data collection—We reviewed the original medical records for all patients identified through the system as having undergone enucleation during the period 1956 through 1988. The demographic and clinical information collected included age, gender, eye, preoperative indication for enucleation, underlying ocular condition leading to enucleation, previous ophthalmic disorders, and preoperative visual acuity of the affected and fellow eyes. Additionally, all pathologic specimens were reviewed and the final diagnosis was confirmed.

Data analysis—The denominators used in the calculation of incidence were based on census data for Olmsted County. Overall incidences were adjusted by age and gender and the gender-specific rates by age to the 1980 white population of the United States. The significance of differences in incidence was assessed using confidence intervals calculated from tables of the cumulative Poisson distribution.[9] Changes in incidence over time were assessed with a trend test.[10]

Results

Incidence—In the 33-year period, 1956 through 1988, 99 residents of Olmsted County (55 males and 44 females) underwent enucleation. Two residents underwent bilateral enucleations, for a total of 101 enucleations. Of the enucleated eyes, 46 were right eyes and 55 were left eyes. The ages at enucleation ranged from 8 months to 87 years (median, 46 years). The mean annual age-adjusted incidence per 100,000 population was 5.17 for males, 3.49 for females, and 4.32 for the total group (95% confidence interval, 3.45 to 5.17). The approximately 50% higher incidence for males contrasted with that for females did reach statistical significance (P = .04). For both genders (Fig. 1), a significant increasing linear trend over age existed (P = .001). The mean annual age- and gender-adjusted incidence decreased over time from 6.82 (95% confidence interval, 4.64 to 8.99) per 100,000 population for the period 1956 through 1966 to 4.07 (95% confidence interval, 2.64 to 5.49) for 1967 through 1977 and 2.80 (95% confidence interval, 1.75 to 3.86) for 1978 through 1988 (P = .001). The decreasing incidence of enucleation over time was isolated to Olmsted County residents who were at least 40 years of age (Fig. 2).

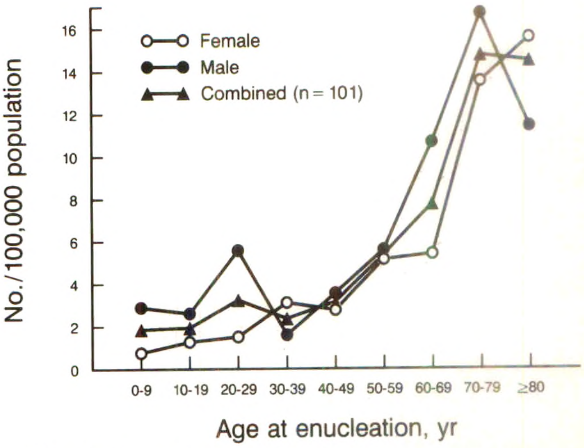


Fig. 1 (Erie and associates). Mean annual incidence of enucleation among residents of Olmsted County, Minnesota, by age and gender, 1956 through 1988.

Visual acuity—Visual acuity of the affected eye before enucleation ranged from 20/20 to no light perception. Visual acuity was 20/40 or better in six patients, 20/30 to 20/100 in four patients, ≤ 20/200 in 87 patients, and unknown in four patients. Visual acuity in the fellow eye at the time of enucleation was 20/40 or better in 70 patients, 20/50 to 20/100 in 11 patients, ≤ 20/200 in 12 patients, and unknown in eight patients. Visual acuity of the remaining eye at last follow-up was 20/40 or better in 57 patients, 20/50 to 20/100 in nine patients, ≤ 20/200 in 18 patients, and unknown in 15 patients. Two patients underwent bilateral enucleations.

Indications—A blind painful eye (62 enucleations) was the most common preoperative reason for enucleation. This was followed by tumor (16 enucleations), acute trauma (12 enucleations), endophthalmitis (five enucleations), corneal ulcer (three enucleations), expulsive choroidal hemorrhage (two enucleations), and sympathetic ophthalmia (one enucleation). Age- and gender-adjusted incidence per 100,000 population for the preoperative reason for enucleation for all years combined (1956 through 1988) was 0.76 (95% confidence interval, 0.39 to 1.13) for tumor, 0.46 (95% confidence interval, 0.19 to 0.72) for acute trauma, and 2.57 (95% confidence interval, 1.91 to 3.23) for blind painful eye. Tumor, acute trauma, and a blind painful eye were the only indications with a significant number of

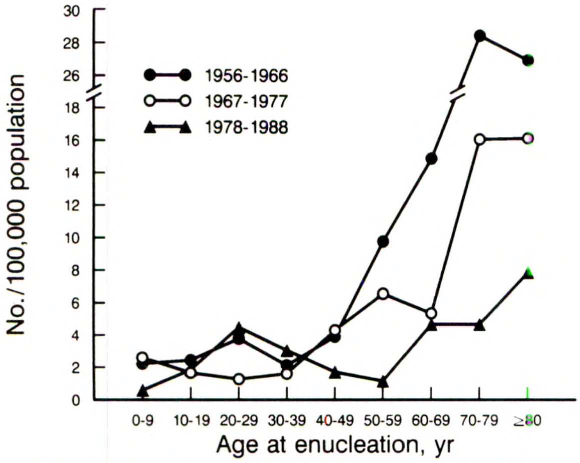
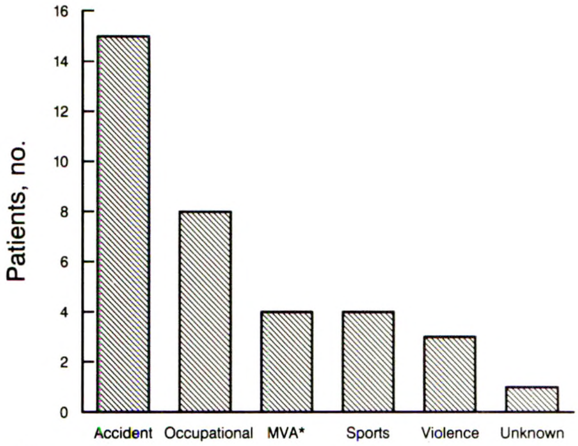


Fig. 2 (Erie and associates). Mean annual incidence of enucleation among residents of Olmsted County, Minnesota, by age, 1956 through 1966, 1967 through 1977, and 1978 through 1988.



*Motor vehicle accident

Fig. 3 (Erie and associates). Distribution of traumatic enucleations among residents of Olmsted County, Minnesota, 1956 through 1988 (MVA indicates motor vehicle accident).

patients to provide estimates. Caution should be used in interpreting the results in the trauma and tumor subgroups, as the number of patients was small.

Age- and gender-adjusted incidence of enucleation for trauma, tumor, and blind painful eye for each 11-year period (that is, 1956 through 1966, 1967 through 1977, and 1978 through 1988) were determined (Table 1). No significant time trends existed for enucleation caused by trauma (P = .25). A decreasing trend existed for tumor but was not statistically significant (P = .11). A 50% decrease in the incidence of enucleation caused by a blind painful eye over these three decades was observed (P = .07).

Age-specific incidence of enucleation for trauma, tumor, and blind painful eye for all years combined (1956 through 1988) were determined (Table 2). A significant increasing linear trend over age existed for tumor (P = .002) and for blind painful eyes (P = .001). No age trend was observed for enucleation caused by trauma.

The underlying ocular condition responsible for the blind painful eye leading to enucleation included remote trauma (23 enucleations), neovascular glaucoma secondary to a central retinal artery or vein occlusion (14 enucleations), neovascular glaucoma secondary to proliferative diabetic retinopathy (eight enucleations), neovascular glaucoma secondary to a chronic unrepairable retinal detachment (seven enucleations), chronic angle-closure glaucoma (four enucleations), end-stage retinopathy of prematurity (three enucleations), congenital glaucoma (one enucleation), chronic uveitis (one enucleation), persistent hyperplastic primary

TABLE 1
AGE- AND GENDER-ADJUSTED INCIDENCE OF PREOPERATIVE REASON FOR ENUCLEATION AMONG OLMSTED COUNTY RESIDENTS, 1956 THROUGH 1988, STRATIFIED BY TIME PERIOD*

	1956 THROUGH 1966		1967 THROUGH 1977		1978 THROUGH 1988	
SUBGROUP	INCIDENCE	(95% C.I.)	INCIDENCE	(95% C.I.)	INCIDENCE	(95% C.I.)
Trauma	0.95	0.16-1.74	0.17	0.07-0.40	0.38	0.01-0.76
Tumor	1.17	0.27-2.06	0.75	0.12-1.37	0.46	0.00-0.92
Blind, painful eye	3.48	1.95-5.01	2.71	1.53-3.87	1.78	0.95-2.62

*Incidence per 100,000 person-years, directly age- and gender-adjusted to the population structure of the 1980 white population; C.I. indicates confidence interval.

TABLE 2

AGE-SPECIFIC INCIDENCE FOR ENUCLEATION BY PREOPERATIVE REASON AMONG OLMSTED COUNTY RESIDENTS, 1956 THROUGH 1988, STRATIFIED BY INDICATION*

	TUMOR			TRAUMA			BLIND, PAINFUL EYE		
AGE GROUP (YRS)	N	INCIDENCE	(95% C.I.)	N	INCIDENCE	(95% C.I.)	N	INCIDENCE	(95% C.I.)
0-9	4	0.74	0.20-1.90	2	0.37	0.05-1.34	2	0.372	0.05-1.34
10-19	0	0.00	—	3	0.65	0.13-1.65	6	1.290	0.47-2.81
20-29	1	0.22	0.00-1.20	5	1.08	0.35-2.52	9	1.943	0.89-3.69
30-39	0	0.00	—	1	0.26	0.01-1.46	8	2.093	0.90-4.12
40-49	1	0.35	0.01-1.95	0	0.00	—	7	2.447	0.98-5.04
50-59	1	0.45	0.01-2.49	0	0.00	—	10	4.467	2.14-8.22
60-69	6	4.18	1.68-8.61	0	0.00	—	5	2.389	0.65-6.12
70-79	3	2.77	0.57-8.09	1	0.92	0.02-5.15	10	8.315	3.81-15.80
80 or older	0	0.00	—	0	0.00	—	5	9.076	2.94-21.20
Total	16	0.76	0.39-1.13	12	0.46	0.19-0.72	62	2.57	1.91-3.23

*Incidence per 100,000 person-years, both genders combined; C.I. indicates confidence interval.

vitreous (one enucleation), and an unsuspected choroidal malignant melanoma (one enucleation).

Traumatic enucleation was classified as acute or remote. Enucleations of traumatized eyes performed within two weeks of the initial injury were considered acute. Twelve of 35 traumatic enucleations (34%) were classified as acute enucleations. Only one enucleation was performed at the initial surgical procedure. Generally, these eyes were enucleated because of a poor visual prognosis and fear of sympathetic ophthalmia. Twenty-three of the 35 traumatic enucleations (66%), however, were caused by remote trauma. These enucleations succeeded the initial injury by a median of 12.5 years (range, six months to 59 years). Generally, these eyes were removed because of pain, usually from increased intraocular pressure, or for cosmetic reasons.

Trauma, therefore, was the underlying reason for enucleation in 35 patients. Twenty-seven of the 35 patients (77%) were males and eight (23%) were females. The median age at enucleation was 25.5 years (range, 3 to 73 years). Trauma was the cause of 12 of the 15 (85%) enucleations performed in the 15 patients in the age group 20 to 29 years. The median age at the time of initial injury was 10 years (range, 1 to 39 years). No documentation of the use of protective eyewear was found for any of the 35 patients injured.

Twenty-three of the 35 (66%) patients who underwent traumatic enucleations were 16 years old or less at the time of initial injury. Fifteen of these injuries occurred at home or play, two occurred at work, two occurred in a motor vehicle accident, two were sports-related, one was caused by a war injury, and one cause was unknown. Twelve (34%) patients were older than 16 years at the time of initial injury. Six of these injuries occurred at work, two were sports-related, two occurred in a motor vehicle accident, one was caused by an assault, and one was war-related (Fig. 3).

Sports-related injuries accounted for 11% of all enucleations after ocular trauma (four of 35 enucleations) and 4% of all enucleations (four of 101 enucleations) over this time period. The median age at enucleation was 22 years (range, 16 to 27 years). The median age at the time of injury was 15 years (range, 10 to 18 years). Two enucleations were caused by BB gun injuries, one by golf, and one by basketball. The basketball-related injury was caused by another player's thumb, which resulted in an irreparable retinal detachment. The patient eventually developed a blind, painful eye secondary to neovascular glaucoma. The golf-related injury occurred when a golf ball directly struck the eye and ruptured the globe. The eye was enucleated because of a poor visual prognosis and fear of sympathetic ophthalmia. The BB gun injuries occurred in two boys who were 10 and 14 years old. Both boys suffered a ruptured globe with an intraocular BB. Both eyes were enucleated approximately ten years after the initial injury secondary to a disfigured, cosmetically unacceptable eye.

Twenty-nine of 101 enucleations (29%) in this time period were caused by neovascular glaucoma. The median age at enucleation for

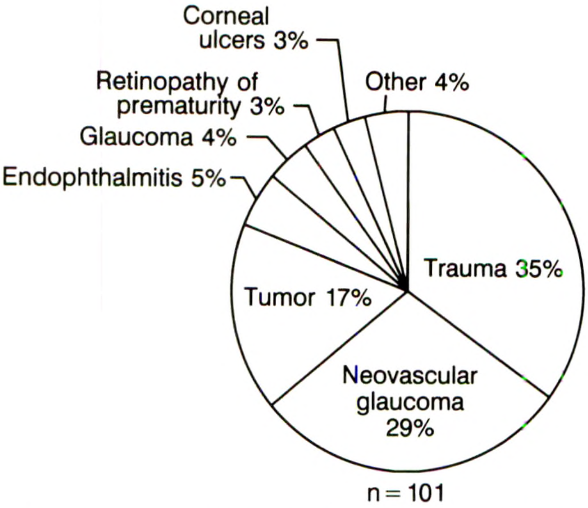


Fig. 4 (Erie and associates). Causes of enucleation among residents of Olmsted County, Minnesota, 1956 through 1988.

neovascular glaucoma was 59 years (range, 11 to 85 years). Eleven of the 29 enucleations were performed in males (38%) and 18 (62%) were performed in females. The mean annual age- and gender-adjusted incidence of neovascular glaucoma-induced enucleation was 1.85 per 100,000 population for the period 1956 through 1966, 1.46 for 1967 through 1977, and 0.82 for 1978 through 1988. Neovascular glaucoma was the reason for 50% (eight of 16) of the enucleations in the age group at highest risk (70 to 79 years). Generally, the eyes were removed for pain, usually from increased intraocular pressure, or for cosmetic reasons. Fourteen of the 29 enucleations (48%) were caused by a central retinal artery or retinal vein occlusion, eight (28%) were caused by proliferative diabetic retinopathy, and seven (24%) were secondary to a chronic, irreparable retinal detachment.

Seventeen enucleated eyes contained an intraocular tumor. Fourteen of the 17 (82%) enucleated eyes contained choroidal melanomas, and three (18%) contained retinoblastomas. The median age at enucleation of the choroidal melanomas was 64.5 years (range, 24 to 87 years). The three patients with retinoblastomas were 8 months, 3 years, and 4 years of age at the time of enucleation, respectively. There was no discrepancy between the clinical and pathologic diagnosis in 16 of the 17 enucleated eyes. However, an unsuspected choroidal melanoma was discovered pathologically in a blind painful eye that had been enucleated in 1959. This case was the only major discrepancy between the clinical and pathologic diagnosis in the entire series (1%).

Five enucleations were performed because of endophthalmitis. Three enucleations succeeded an intracapsular cataract extraction, one succeeded a full-thickness filtering procedure, and one was caused by *Toxocara*-induced endophthalmitis. The median age at enucleation was 66 years (range, 9 to 74 years).

Trauma (35 enucleations), including both acute and remote enucleations, was the most common underlying reason for enucleation in this time period. Neovascular glaucoma (29 enucleations) caused by vascular occlusive disease, proliferative diabetic retinopathy, or chronic retinal detachment was the second most common reason for enucleation. This was followed by intraocular tumors (17 enucleations), endophthalmitis (five enucleations), angle-closure glaucoma (four enucleations), retinopathy of prematurity (three enucleations), corneal ulcer (three enucleations), expulsive choroidal hemorrhage (two enucleations), congenital glaucoma (one enucleation), chronic uveitis (one enucleation), and persistent hyperplastic primary vitreous (one enucleation; Fig. 4).

Discussion

Long-term time trends in the incidence of enucleation have not been well studied in the United States. In this regard, the Rochester Epidemiology Project–linked medical record system is particularly well suited for population-based studies of selected ophthalmic conditions.[7,8,11] Over the 33-year period of this study, 101 enucleations were performed in the population of Olmsted County. The mean annual incidence of enucleation for all ages was 4.32 per 100,000 population, with age and gender adjusted to the 1980 United States white population. The age-adjusted incidence was approximately 50% higher in men (5.17 per 100,000) than it was in women (3.49 per 100,000; P = .04). The age- and gender-specific incidence of enucleation increased continuously with increasing age, peaking at ages 70 to 79 years (P = .002). Trauma, neovascular glaucoma, and tumor were the most common preoperative reasons for enucleation.

The mean annual age- and gender-adjusted incidence of enucleation decreased continuously over time (P = .01). This decreasing incidence of enucleation over time was isolated to Olmsted County residents who were at least 40 years of age (Fig. 2). The highest annual incidence of enucleation, however, was among those people older than 50 years of age (Fig. 1).

Evisceration, exenteration, and retrobulbar alcohol injection for relief of pain are surgical procedures that could affect the rate of enucleation in a defined population. In our community, however, enucleation appears to be the preferred procedure, as only seven eviscerations and one exenteration were performed in the population of Olmsted County during this study period. The incidence of retrobulbar alcohol injections was not determined.

Neovascular glaucoma was a significant cause of enucleation in our community during this study period. This has not been evident in earlier surveys at tertiary care centers or eye hospitals.[1,3-5] Neovascular glaucoma was responsible for 50% of enucleations (eight of 16) in Olmsted County residents who were between 70 and 79 years of age. Sixty-nine percent (20 of 29) of neovascular glaucoma-related enucleations were caused by a central retinal artery or vein occlusion or proliferative diabetic retinopathy.

The incidence of neovascular glaucoma-related enucleations has decreased by more than 50% over the past 30 years in this community, especially in the last decade. Diffusion into routine clinical practice in this community of the successful use of laser photocoagulation in preventing neovascular glaucoma after central retinal vein or artery occlusions[12] and proliferative diabetic retinopathy[13] may be responsible for this decreasing time trend.

Although not statistically significant, a decreasing time trend was observed for tumor-related enucleations (P = .11). This decreasing trend may have been caused in part by the increasing use of radiotherapy in the treatment of choroidal melanomas in the study period.[14] Additionally, a definite trend away from enucleation has developed in the treatment of retinoblastomas in recent years.[15]

Consistent with other surveys,[1,3-5] trauma was the most common cause of enucleation with the incidence peaking at 20 to 29 years. Although decreasing time trends were found for tumor and neovascular glaucoma-related enucleations, no significant time trends existed for traumatic enucleation (P = .46). Sixty-six percent (23 of 35) of patients who underwent traumatic enucleations were 16 years old or younger at the time of initial injury. Forty-three percent (15 of 35) of these injuries were accidental, occurring at home or play. No documentation of the use of protective eyewear was found for any of the injured patients.

Sports-related enucleations accounted for 11% (four of 35) of all enucleations after ocular trauma. Despite the popularity of racquet and ball sports, it is noteworthy that no racquetball, tennis, softball, or hockey injury resulted in enucleation. In the Olmsted County community, sports-related ocular injuries are more often characterized by hyphema.[11]

Our population-based study of enucleation supports the growing impression that ocular trauma is a marked yet preventable threat to the ocular well-being of people of all ages, but especially to children. Unfortunately, the incidence of traumatic enucleations among Olmsted County residents has not significantly decreased over this 33-year study period. Overall, the incidence of enucleation has decreased over time primarily because of the decreasing incidence of neovascular glaucoma and tumor-related enucleations, consistent with changes in ophthalmic care in this community over the past three decades.

References

1. Lim, J. K., and Cinotti, A. A.: Causes for removal of the eye. A study of 890 eyes. Ann. Ophthalmol. 8:865, 1976.

2. Apt, L., and Sarin, L. D.: Causes of enucleation of eyes of infants and children. JAMA 181:948, 1962.

3. Anderson, W. D., and Passmore, J. W.: Enucleation in military personnel. Milit. Med. 131:281, 1968.

4. Batten, K. L.: Causes of enucleation as seen in Jerusalem. Br. J. Ophthalmol. 55:174, 1971.

5. Davenger, M.: Causes of enucleation in Uganda. Br. J. Ophthalmol. 54:252, 1970.

6. Margo, C. E.: Surgical enucleation in community hospitals. Am. J. Ophthalmol. 108:452, 1989.

7. Kurland, L. T., and Molgaard, C. A.: The patient record in epidemiology. Sci. Am. 245:54, 1981.

8. Kurland, L. T., Elveback, L. R., and Nobrega, F. T.: Mayo Clinic records linkage system in the Rochester-Olmsted Epidemiology Program Project. In Davies, A. M. (ed.): Uses of Epidemiology in Planning Health Services. Belgrade, Savremena Administraciga, 1973, pp. 164–176.

9. Beyer, W. H. (ed.): CRC Handbook of Tables for

Probability and Statistics. Cleveland, Ohio, Chemical Rubber Co., 1966, pp. 58–64.

10. Armitage, P.: Tests for linear trends in proportions and frequencies. Biometrics 11:375, 1955.

11. Kennedy, R. H., and Brubaker, R. F.: Traumatic hyphema in a defined population. Am. J. Ophthalmol. 106:123, 1988.

12. Magargal, L. E., Brown, G. C., and Augsburger, J. J.: Efficacy of panretinal photocoagulation in preventing neovascular glaucoma following ischemic central retinal vein obstruction. Ophthalmology 89:780, 1982.

13. Diabetic Retinopathy Study Group: Photocoagulation treatment of proliferative diabetic retinopathy. The second report of diabetic retinopathy study findings. Ophthalmology 85:82, 1978.

14. Augsburger, J. J., Gamel, J. W., Sardi, V. F., Greenberg, R. A., Shields, J. A., and Brady, L. W.: Enucleation vs. cobalt plaque radiotherapy for malignant melanomas of the choroid and ciliary body. Arch. Ophthalmol. 104:655, 1986.

15. Shields, J. A., Shields, C. L., and Sivalingam, V.: Decreasing frequency of enucleation in patients with retinoblastoma. Am. J. Ophthalmol. 108:185, 1989.

OPHTHALMIC MINIATURE

The other woman was much smaller and slighter. She sat huddled in an arm-chair near the stove, and when I came in she turned her head quickly toward me, without the least corresponding movement of her body. Her hair was as grey as her companion's, her face as bloodless and shrivelled, but amber-tinted, with swarthy shadows sharpening the nose and hallowing the temples. Under her shapeless dress her body kept its limp immobility, and her dark eyes had the bright witch-like stare that disease of the spine sometimes gives.

Edith Wharton, *Ethan Frome*
New York, Charles Scribner's Sons, 1911, p. 173-174

Trabeculectomy Without Conjunctival Incision

E. Michael Van Buskirk, M.D.

A trabeculectomy technique with conventional instruments, but without conjunctival incision or intracameral manipulation, was completed in 12 eye-bank eyes, two cat eyes, and in five patients with glaucoma. A partial-thickness limbal corneal flap provided access to an intrastromal limbal pocket through which the subconjunctival space was entered with an irrigating cystotome. The anterior chamber was entered at the surgical corneoscleral limbus beneath the corneal flap and the peripheral iridectomy was completed without difficulty. Full-thickness or guarded limbal fistulas could be created. Guarded limbal fistulas were completed in five of five patients with glaucoma. The technique produced low-lying, diffuse filtration blebs that persisted throughout the three-month postoperative period and reduced mean intraocular pressure from 33 to 12 mm Hg. Corneal trabeculectomy holds promise as a method for a filtration operation that does not require conjunctival incision, intracameral manipulation, or costly technology.

SUCCESSFUL FILTRATION operations to reduce intraocular pressure in glaucoma involve creation of a fistula through the eye wall from the anterior chamber to a subconjunctival aqueous reservoir.[1,2] Most conventional filtration operations involve a translimbal fistula, with or without a partial-thickness scleral flap.[3] Filtration failure often derives from progressive contracture of the filtration bleb for various reasons that are related to subconjunctival and conjunctival scarring or occlusion of the limbal fistula, or both.[2] To provide access to the surgical corneoscleral limbus for creation of the limbal fistula, incision of the conjunctiva has generally been necessary either at the corneoscleral limbus to create a fornix-based flap, or distal to the corneoscleral limbus to create a limbal-based flap.

Because filtration failure often relates to scarring within the conjunctiva, episclera, and surrounding tissues, creation of filtration fistulas to the subconjunctival space without violating the conjunctiva has been attempted.[2] Scheie,[4] in the early 1950s, used a transcameral goniopuncture approach to enter the subconjunctival space. The availability of laser and other technologic advances in recent years has renewed interest in this concept.[5-8] However, goniopuncture with old or new technology poses several problems. To penetrate the corneoscleral limbus, it is necessary either to pass an instrument across the anterior chamber and penetrate from an ab interno approach or to pass a probe under the conjunctiva through ill-defined limbal landmarks for a more conventional ab externo approach. Performance of iridectomy becomes difficult. Because of these limitations, it seems worthwhile to endeavor to produce a limbal filter that avoids conjunctival incisions and intracameral manipulation, as well as expensive technologic processes.

Cairns[9] described performance of trabeculectomy by means of a corneal incision without violating the conjunctiva, but relied upon ostia of scleral perforating vessels to provide access to the subconjunctival space. I have modified Cairns' corneal trabeculectomy approach to provide fistulization to the subconjunctival space from the anterior chamber with iridectomy but without incising or violating the conjunctiva.

Material and Methods

The superior limbal area was examined to identify a relatively hypovascular area, usually in the supranasal or supratemporal quadrant. A trapezoidal flap of peripheral cornea was prepared 3 mm in width at the base, 2 mm in width

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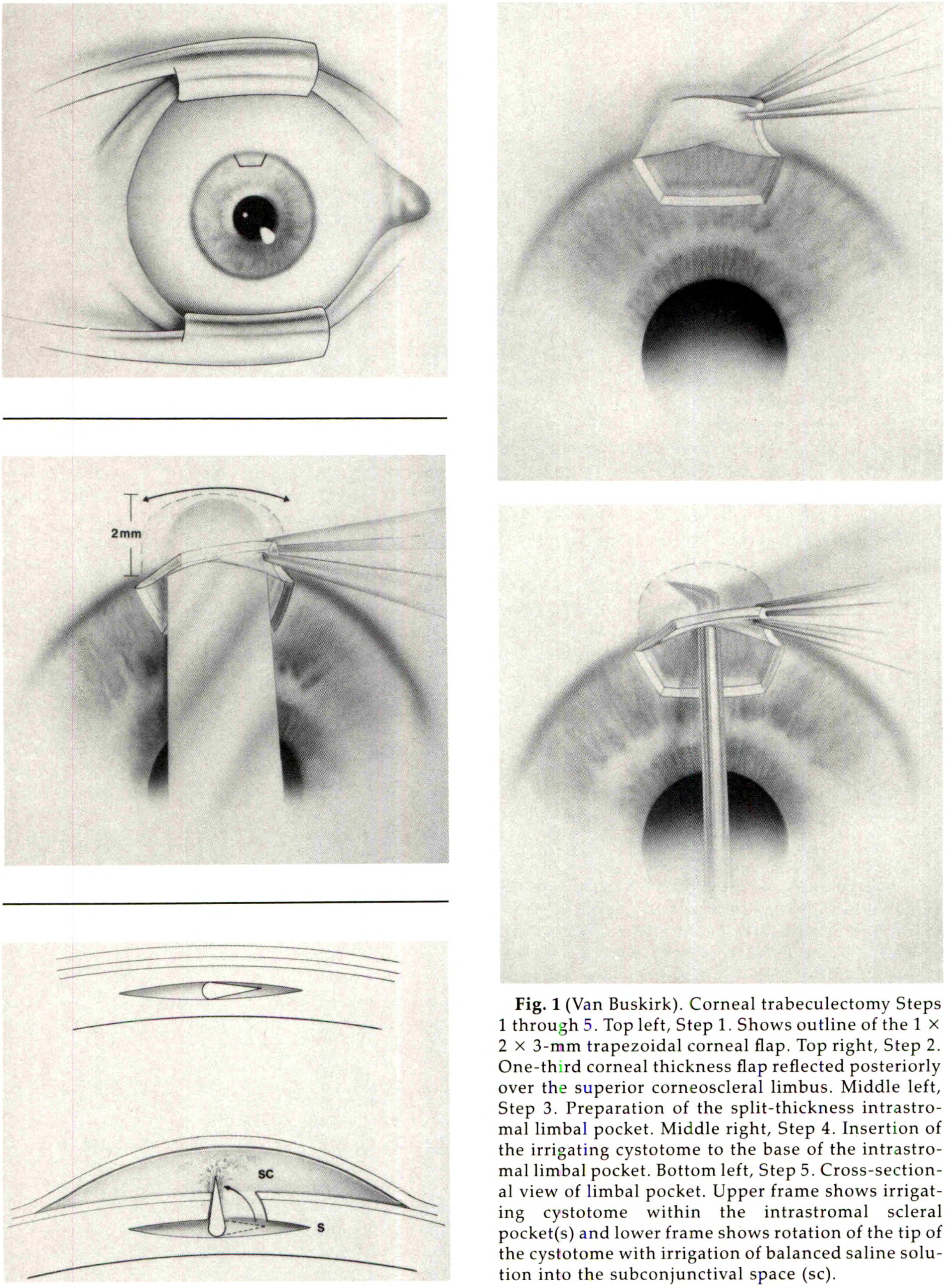
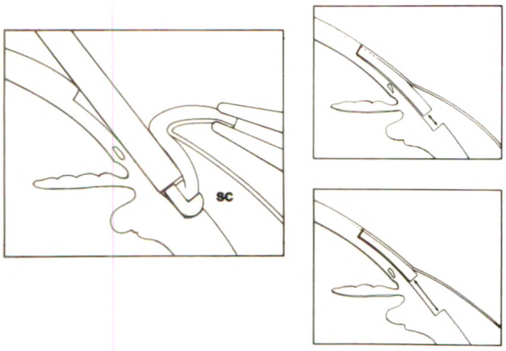
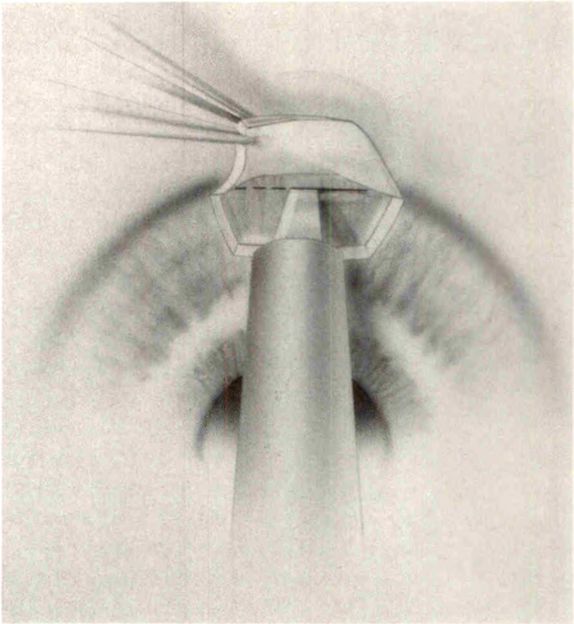
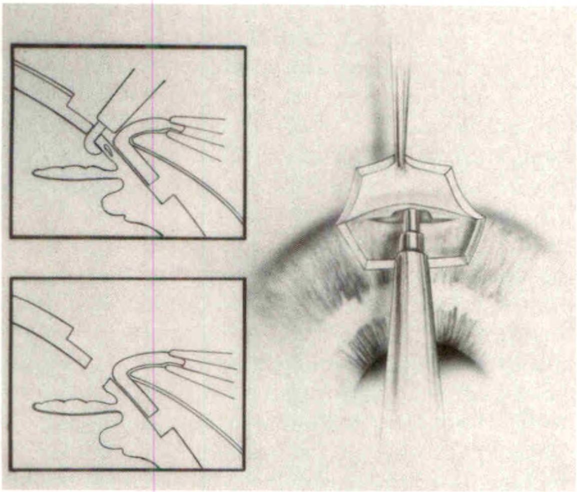
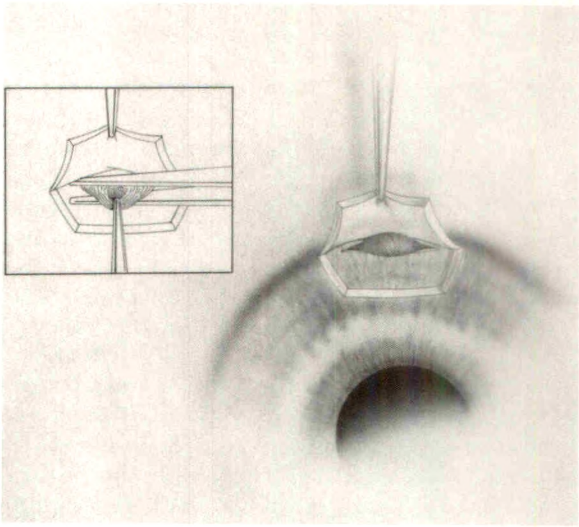


Fig. 1 (Van Buskirk). Corneal trabeculectomy Steps 1 through 5. Top left, Step 1. Shows outline of the 1 × 2 × 3-mm trapezoidal corneal flap. Top right, Step 2. One-third corneal thickness flap reflected posteriorly over the superior corneoscleral limbus. Middle left, Step 3. Preparation of the split-thickness intrastromal limbal pocket. Middle right, Step 4. Insertion of the irrigating cystotome to the base of the intrastromal limbal pocket. Bottom left, Step 5. Cross-sectional view of limbal pocket. Upper frame shows irrigating cystotome within the intrastromal scleral pocket(s) and lower frame shows rotation of the tip of the cystotome with irrigation of balanced saline solution into the subconjunctival space (sc).









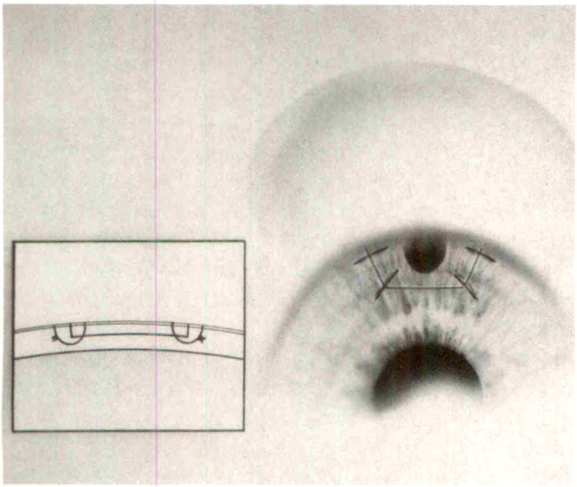


Fig. 2 (Van Buskirk). Corneal trabeculectomy Steps 6 through 10. Top left, Step 6. Cross-sectional drawing showing insertion of Kelley punch into the internal pocket to remove a bite from its external wall to create the external portion of the limbal fistula to the subconjunctival space (sc). The upper inset shows a single bite to create a guarded fistula and the lower inset shows several bites to create a full-thickness fistula. Top right, Step 7. Ab externo incision into anterior chamber at the surgical corneoscleral limbus. Middle left, Step 8. Punch removing two bites from the posterior lip of the incision to create the internal aspect of the fistula. Superior inset shows punch in wound and lower inset shows offset between internal and external segments of the fistula. Middle right, Step 9. Iridectomy. Bottom left, Step 10. Four 10-0 nylon sutures closing corneal flap. Inset shows sutures through the corneal dissection bed.

at the apex, and 1 mm in height, hinged at the corneoscleral limbus (Fig. 1). A spatula blade was then used to dissect the flap toward the corneoscleral limbus from the underlying corneal bed at approximately one-third corneal thickness (Fig. 1). The spatula blade then advanced the planar incision posterior to the corneoscleral limbus, creating an intrastromal limbal pocket extending within the scleral stroma approximately 1.5 to 2.0 mm posterior to the anterior insertion of the conjunctiva and 3 mm in width (Fig. 1). A specially designed irrigating cystotome was fabricated by bending the beveled tip of a 25-gauge hypodermic needle over its lumen in such a way to direct the jet of irrigation fluid perpendicularly to the shaft of the needle and parallel to the cutting blade of the needle. This instrument was passed into the intrastromal pocket to its apex, approximately 2 mm posterior to the anterior insertion of the conjunctiva (Fig. 1). While irrigating, the needle cystotome was rotated 90 degrees to allow the tip to enter the subconjunctival space and simultaneously to inject balanced saline solution creating a subconjunctival, fluid-filled reservoir (Fig. 1). With a slight side-to-side motion, the cystotome blade was used to enlarge the incision to approximately 2 mm in width. A Kelley Descemet's membrane punch was then passed into the intrastromal pocket and one bite was taken from the anterior lip of the partial-thickness scleral wound, to create a 1.0- × 0.5-mm semilunar fistula from the subconjunctival space to the intrastromal pocket (Fig. 2). After removal of the punch, the corneal flap was then reflected over the corneoscleral limbus and the anterior extent of the surgical blue zone was identified. At the junction of the blue limbal transition zone and transparent cornea, an ab externo incision, 2 mm in length, was made into the anterior chamber (Fig. 2). Two bites were taken from the posterior lip of this wound with a Kelley Descemet's membrane punch to create the inner aspect of the fistula (Fig. 2). The iris prolapsed spontaneously into the wound and a peripheral iridectomy was performed in the conventional manner (Fig. 2).

The corneal flap was then replaced to its normal anatomic position. Using a sharply curved cutting needle (192101 with CU-5 needle, Alcon Laboratories, Ft. Worth, Texas) on a 10-0 nylon suture, the corneal flap was sutured at each of the four corners of the corneal flap (Fig. 2). By tying the sutures tightly at the base of the flap, the cord length between them completely occluded the fistular communication with the intracorneal space and the conjunctival bleb developed spontaneously. To achieve a water-tight closure, it was necessary for the suture to pass through the bed of the corneal dissection plane. Two additional sutures, placed along the anterior extent of the corneal flap, achieved complete anatomic closure. The knots were rotated to bury them within the corneal stroma.

An intracameral paracentesis was performed before the anterior chamber was entered in all eyes and the anterior chamber was deepened through the paracentesis wound at the conclusion of the procedure.

Eye-bank eyes—Twenty-eight eye-bank eyes were used to develop the procedure with 12 eyes subjected to the exact technique described. Human eye-bank eyes that possessed some residual perilimbal conjunctiva were placed in a 30-ml medicine cup wrapped in gauze moistened with saline solution. A 23-gauge needle swaged on polyethylene tubing and connected to a 50-ml saline solution reservoir was passed through a paracentesis wound to the anterior chamber through the pupil to rest in the posterior chamber. The reservoir was elevated approximately 50 cm above the corneoscleral limbus to simulate increased intraocular pressure and to provide aqueous outflow. The technique described was performed. The saline solution in the reservoir was then aspirated and replaced with 10% buffered formaldehyde, which was perfused into the anterior chamber and through the filtration fistula. After one hour, the globes were removed from the apparatus and immersed in 10% buffered formaldehyde. Subsequently, the globes were dehydrated in graded alcohols, embedded in paraffin, sectioned at 7 μm, and stained for light-histologic examination.

Cat eyes—The procedure was then repeated in two cat eyes as a terminal experiment to assure that it was technically feasible in the living eye. At the completion of the procedure, the anterior chamber was infused with 10% buffered formaldehyde. After one hour of fixative infusion, the globes were enucleated and the eyes were prepared for histologic examination in the same manner as were the eye-bank eyes.

Patients with glaucoma—The procedure was then applied to five patients with glaucoma, aged 46 to 76 years, who met conventional criteria for filtration operations, with uncontrolled intraocular pressure on maximally tolerated medical or laser treatment, or both. Only one patient had primary open-angle glaucoma. The others had chronic angle closure, pseudoexfoliation, pigmentary glaucoma, and uveitis associated with sarcoidosis and pseudophakia. Patients achieved conventional local and retrobulbar anesthesia. No bridle fixation suture was used. Three patients less than 50 years of age were treated adjunctively with 5-fluorouracil on the basis of age or diagnosis of secondary glaucoma. Each was monitored at least three months postoperatively.

Results

Eye-bank eyes—Once the technique was developed in the first 16 eyes in which various changes were made, a bleb developed uniformly in 12 of 12 eye-bank eyes after completion of the procedure. Histologic characteristics of the fistula and the iridectomy were observed in one of the eye-bank eyes (Fig. 3). A fistula from the anterior chamber to the internal portion of the intrascleral pocket was observed in the conventional position at the anterior portion of the trabecular meshwork to the peripheral cornea. The external portion of the fistula, from the intrastromal pocket to the subconjunctival space, is posteriorly offset from the internal fistular segment to create a guarded effect. The degree of guarding could be adjusted by removing additional portions of the external limbal wall of the intrascleral pocket with the Kelley punch. The iridectomy underlay the internal aspect of the fistula.

Cat eyes—The procedure was also completed without complication in cat eyes with immediate development of the subconjunctival reservoir. Because these were terminal experiments, no long-term follow-up of the bleb was available. Histologic characteristics of the cat eyes immediately after the procedure were similar to those of the human eye-bank eyes. The inner and outer segments of the fistula were again offset, but with full development of a subconjunctival bleb. Because of the prominent major

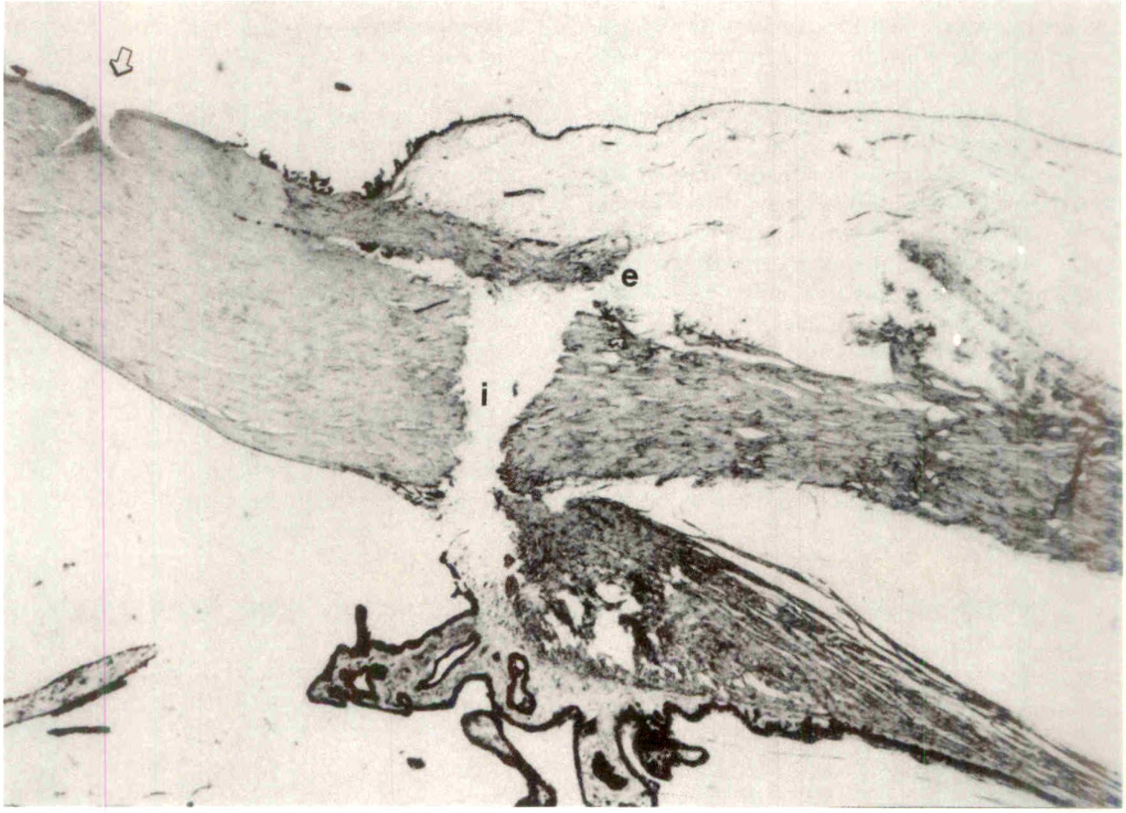


Fig. 3 (Van Buskirk). Histologic cross section of corneal trabeculectomy in an eye-bank eye showing corneal incision (arrow), internal filtration segment (i), and external filtration segment (e) with subconjunctival filtration bleb (× 35).

circle of the iris on the periphery of the cat iris, no iridectomy was attempted.

Human patients—The procedure was completed technically in all five patients described. Touching the conjunctiva at all during the procedure was not necessary except with fixation forceps during the paracentesis. Rotation of the angled irrigating cystotome tip into the subconjunctival space was accomplished without difficulty in all patients, with no threat of conjunctival perforation. The ability to distend the subconjunctival space markedly assures full scleral penetration with the needle tip. A relatively hypovascular area of the corneoscleral limbus was selected, although one patient (Case 2) had prominent episcleral veins and another patient (Case 1) had undergone a cataract operation. Only one patient (Case 5) had any episcleral bleeding from the cystotome incision, which manifested as fine oozing to form a 5-mm-diameter subconjunctival hemorrhage that stopped bleeding spontaneously and was completely dissipated six hours postoperatively. No cautery was needed or used on any of the five patients.

The internal aspect of the fistula was also completed without difficulty. Because of the hypothetical necessity to place the fistula posterior to the cord length of the base of the corneal flap, the surgical exposure of the fistular site is not as good as with conventional trabeculectomy. The anterior extent of the surgical corneoscleral limbus was easily identifiable as an abrupt transition from gray limbal stroma to clear cornea just posterior to the cord length between the peripheral extremes of the corneal flap edges. Placing the incision to the anterior chamber at this transition line allowed placement of the fistula over the anterior trabecular meshwork. Simultaneous with placement of the two basal nylon sutures, the bleb developed spontaneously in all cases. The corneal wound did not leak in any patient after placement of all four sutures. Wound integrity was further tested in all patients with deepening of the anterior chamber through the paracentesis wound. The procedure required approximately 20 minutes to complete.

Postoperative intraocular pressure data on each patient were determined (Table). The mean preoperative intraocular pressure with hypotensive medication was 33 mm Hg (range, 18 to 52 mm Hg) and was 12 mm Hg (range, 8 to 17 mm Hg) three months postoperatively, without the use of any hypotensive medications. All patients developed obvious but diffuse subconjunctival blebs during the first few postoperative hours. Subjectively, postoperative inflammation, especially conjunctival inflammation, was minimal with only mild erythema from the first postoperative day (Fig. 4).

The blebs in the five patients uniformly remained diffuse and covered more than one quadrant of the globe by the first week. They rapidly developed a mature hypovascular appearance with multiple microcystic changes of filtration. Leakage was not evident in any of the corneal wounds at the immediate conclusion of the procedure or during the postoperative period despite vigorous Seidel testing. The anterior corneal sutures were removed six weeks postoperatively.

One of the five patients developed a transient intraocular pressure increase to 20 mm Hg during the second to the fourth week. Although this patient's bleb remained diffuse, some central membranous structures were visible in its central portion. After the fourth week, the intraocular pressure diminished to 16 mm Hg.

Complications—No flat anterior chambers developed, although Patient 4 developed an ophthalmoscopically identifiable choroidal detachment associated with a transient (seven days' duration) shallowing to approximately one half the normal depth of the anterior chamber.

Corneoscope photography disclosed compar-

TABLE

INTRAOCULAR PRESSURE (MM HG) RESPONSE TO CORNEAL TRABECULECTOMY IN FIVE PATIENTS

		AFTER TRABECULECTOMY					
CASE NO.	BEFORE TRABECULECTOMY	2 DAYS	1 WEEK	2 WEEKS	1 MONTH	2 MONTHS	3 MONTHS
1	52	5	4	12	16	17	17
2	18	0	6	16	12	14	14
3	24	4	6	8	8	10	12
4	33	0	2	2	7	8	8
5	37	15	14	11	10	9	11

ative flattening of the cornea over the wound with no or minimal distortion of the central four mires. Effects of the procedure on corneal astigmatism will be the subject of a separate study, but preliminary results suggest no lasting effects after suture removal six weeks postoperatively. No marked change in refraction developed in any patient after three months of follow-up.

Because of forceps manipulation, transient corneal epithelial defects over the corneal flap developed in all patients and two had similar localized defects along the wound of the surrounding cornea. This healed promptly in four of the five patients but persisted for two weeks in Patient 1, who also was treated adjunctively with 5-fluorouracil. This patient was pseudophakic and had chronic uveitis and sarcoidosis and a compromised corneal endothelium. At the conclusion of the procedure, two subsequent patients received a sterile disposable soft contact lens that was removed on the second postoperative day.

Discussion

The data from our few patients must be considered preliminary. However, the study has shown the feasibility of a translimbal fistulizing procedure with conventional instrumentation that does not violate the conjunctiva or anterior chamber in experimental eye-bank and living cat eyes and in human patients.

The corneal trabeculectomy can produce intraoperative filtration blebs that persist at least through the first three postoperative months. The intraocular pressure was reduced to values between 10 and 17 mm Hg in the five patients without ocular hypotensive medications. Once the techniques are learned, the procedure can be completed rapidly because no conjunctival dissection is necessary. The iridectomy can be performed in the conventional manner without difficulty and without compromising the surgeon's usual technique. The procedure can be completed with conventional instruments and does not require expensive equipment. By adjusting the offset between the inner and outer segments of the fistula, the procedure can create varying degrees of guarded or full-thickness fistulas. Because of the availability of instrumentation, the procedure could be performed in less-industrialized areas of the world without compromise of technique.

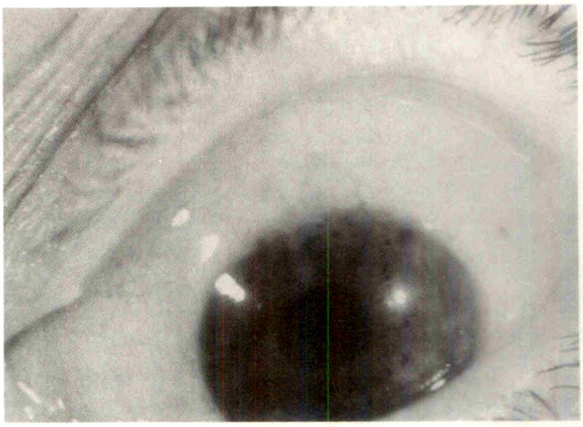


Fig. 4 (Van Buskirk). Case 5. External photograph on the ninth postoperative day showing filtration bleb and absence of conjunctival erythema.

This procedure could offer some potential advantages over conventional filtration operations. If incision and manipulation of conjunctiva serves as a stimulus for subconjunctival fibrosis and bleb failure, the corneal approach markedly minimizes this stimulus. The conjunctiva is not touched during the procedure. The glistening spatula blade used for the lamellar corneal and scleral dissection can be easily seen through the superficial scleral layers to verify the depth of the limbal pocket posterior to the insertion of Tenon's capsule. By selecting a relatively avascular site for the intralimbal lamellar dissection, no remarkable subconjunctival bleeding was encountered even in the two patients with relatively prominent episcleral veins (Cases 1 and 2). Little bleeding is encountered, and no or minimal cautery is needed. The only potential bleeding sites are perforating scleral vessels in preparation of the scleral pocket and at the base of the iris during the iridectomy.

On the negative side, the standards to which this or any new glaucoma procedure are compared are high. Conventional trabeculectomy works well in most subjects.[3] The corneal procedure is not technically easy to accomplish the first time. The instruments are held facing the surgeon operating at the superior corneoscleral limbus, opposite to the usual position. The entire procedure is completed within the confines of a 3-mm corneal lamellar incision, leaving little margin for error. Undue manipulation of the cornea may lead to epithelial defects that may compromise the ability to use adjunctive antimetabolites. This potential problem can be alleviated by the use of a bandage soft-contact lens or a collagen shell placed at the conclusion of the operation or during the postoperative period.

Some subtle technical challenges also exist. Although it is tempting to place the fistula in the base of the corneal flap dissection, the anterior edge of the fistula must be posterior to the cord length between the most peripheral arms of the corneal flap incision. If not, eye-bank eye work suggested that intrastromal corneal leaking would occur, although corneal wound leaking was not evident in any of the surgical patients. This relative posterior location compromises visibility of the intracameral incision and makes insertion of the Kelley punch more difficult. It is also essential that the basal sutures be placed adjacent to the conjunctival insertion to prevent limbal wound leak. However, with practice in eye-bank eyes, this procedure should be technically easy to perform by any ophthalmic microsurgeon. It can be completed in a relatively short time.

The 3-mm width at the base of the flap was selected carefully as a compromise between adequate surgical exposure and access to the surgical corneoscleral limbus. Greater than 3-mm width anteriorly displaces the cord length at the reflection of the corneal flap to observe exposure of the surgical blue zone. A smaller flap does not permit adequate side-to-side motion for safe preparation of the scleral pocket. The corneal flap is placed far peripherally so there is little potential for astigmatism.

The postoperative course typical of conventional filtration procedures was followed in these five patients: low diffuse filtration blebs and relatively soft eyes initially. Because they exhibit translimbal filtration to a subconjunctival reservoir, the usual postoperative complications of filtration could be anticipated in future cases such as flat anterior chamber with serous or hemorrhagic choroidal detachment. Fashioning a guarded fistula by preserving the anterior-posterior offset between the inner and outer segments of the fistula, as done in the five patients described, appears to inhibit these complications (Fig. 2). However, the fistula can be converted to full thickness simply by taking additional punch bites from the external wall of the limbal stromal pocket to eliminate the segment offset (Fig. 2). In such patients, all the increased complications of full-thickness filtration would be expected.

The reduced conjunctival inflammation and erythema is the most obvious, but subjective, difference from conventional filtration operations. This may account for the observation in all cases of diffuse blebs covering a minimum of one quadrant, two or more quadrants in three of the five. The absence of conjunctival incision may sufficiently minimize the conjunctival wound healing to inhibit development of circumscribed blebs. The first patient (Case 1) had undergone a previous conjunctival operation (cataract) and did have more episcleral erythema, and ultimately more membrane proliferation, postoperatively than did the other patients.

Cairns[9] described a similar clear cornea approach to trabeculectomy that apparently did not achieve much success or acceptance. In contrast, the cystotome and punch incision from the intrastromal pocket into the subconjunctival space differentiates the corneal trabeculectomy described from the Cairns approach. Further, creation of two offset fistula segments from the anterior chamber to the subconjunctival space achieves the same kind of free but guarded access of aqueous humor to the bleb cavity as with conventional trabeculectomy.

Various technologies are now available for production of filtration with no or minimal conjunctival manipulation.[5-8] The potential advantages of the corneal approach as well as of the new technical approaches are based upon the assumption that conjunctival incisions serve as a stimulus to scarring and filtration failure. Although several arguments underpin this hypothesis, no hard data prove its validity. Much of the new technology for laser or mechanical fistulization is based upon acceptance of the validity of this hypothesis. These include a plethora of technical and sophisticated instruments.[5-8] Before this new technology takes on a discipline of its own, its raison d'être—to provide a better, safer, and easier filtration procedure—should be recalled. With increased national socioeconomic pressure to diminish health care expenses, reduced cost will be an additional incentive influencing any new surgical technologic processes.

Most of the new technologic variants pose potential disadvantages and unsolved problems. They lead to full-thickness limbal fistulas that presumably would be associated with the following complications attendant to these procedures: flat anterior chamber, suprachoroidal hemorrhage, and thin-walled localized limbal blebs. Many require insertion of instruments across the anterior chamber that may lead to lens injury with sudden decompression of the globe, and also may pose a strong stimulus toward a wound-healing response. With other techniques, the need to pass instruments subconjunctivally may obviate the potential advantages of the new technologic processes by violating the conjunctiva. The difficulty in performing an iridectomy safely also undermines the potential advantages of some new approaches.

Perhaps most ominous for the new fistulization technologies is cost. As United States health care places an ever higher premium on efficiency and cost containment, the application of excessively expensive, unifunctional technical instruments may soon prove anachronistic.

Although no long-term follow-up is available for corneal trabeculectomy, these preliminary studies have shown the feasibility of performing filtration with conventional instrumentation, without conjunctival incision, and without compromise of the iridectomy. Filtration blebs have developed readily and the initial postoperative course has been typical of that following conventional trabeculectomy.

References

1. Addicks, E. M., Quigley, H. A., Green, W. R., and Robin, A. L.: Histologic characteristics of filtering blebs in glaucomatous eyes. Arch. Ophthalmol. 101:795, 1983.
2. Maumenee, A. E.: External filtering operations for glaucoma. The mechanism of function and failure. Trans. Am. Ophthalmol. Soc. 58:319, 1960.
3. Lewis, R. A., and Phelps, C. D.: Trabeculectomy vs. thermosclerostomy. A five-year follow-up. Arch. Ophthalmol. 102:533, 1984.
4. Scheie, H. G.: Goniopuncture. A new filtering operation for glaucoma. Preliminary report. Arch. Ophthalmol. 44:761, 1950.
5. March, W. F., Gherezghiher, T., Koss, M. C., Shaver, R. P., Heath, W. D., and Nordquist, R. D.: Histologic study of a neodymium:YAG laser sclerostomy. Arch. Ophthalmol. 103:860, 1985.
6. Latina, M., Goode, S., de Kater, A. W., Long, F. H., Deutsch, T. F., and Epstein, D. L.: Experimental ab interno sclerotomies using a pulsed dye laser. Lasers Surg. Med. 8:233, 1988.
7. Brown, R. H., Denman, D. B., Bruner, W. E., Lynch, M. G., Quigley, H. A., and Parel, J.-M.: Internal sclerectomy for glaucoma filtering surgery with an automated trephine. Arch. Ophthalmol. 105:133, 1987.
8. Hoskins, H. D., Jr., Iwach, A. G., Drake, M. V., Schuster, B. L., Vassiliadis, A., Crawford, J. B., and Hennings, D. R.: Subconjunctival THC:YAG laser limbal sclerostomy ab externo in the rabbit. Ophthalmic Surg. 22:589, 1991.
9. Cairns, J. E.: Clear-cornea trabeculectomy. Trans. Ophthalmol. Soc. U.K. 104:142, 1985.

Reformulation and Drop Size of Apraclonidine Hydrochloride

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We performed a prospective, double-masked, placebo-controlled, six-period, cross-over study in which normal subjects were randomly assigned to treatment and compared three different formulations of apraclonidine hydrochloride (the present commercially available formulation, and formulations with hydroxypropylmethylcellulose or lysolecithin). We also evaluated the efficacy of a 16-μl and 30-μl drop size. The magnitude and duration of decrease in intraocular pressure was comparable for all formulations. Most subjects tolerated all formulations well with only a few reporting any side effects. The best-tolerated formulation was 0.5% apraclonidine hydrochloride delivered with a 16-μl drop size. Dry mouth developed frequently with the commercially available 1% apraclonidine solution. Blurred vision complicated the use of the formulation containing hydroxypropylmethylcellulose. Both dry mouth ($P < .05$) and blurred vision ($P = .004$) were statistically significant side effects.

APRACLONIDINE HYDROCHLORIDE is a relatively selective alpha$_2$-adrenergic agonist and a clonidine derivative. Topical 1.0% apraclonidine is the only medication that consistently reduces intraocular pressure increases accompanying argon laser trabeculoplasty and iridotomy.[1-4] Various concentrations of apraclonidine have reduced intraocular pressure in normal and glaucomatous eyes.[5-8] Dose-related[7] side effects, such as dry mouth, might limit its long-term usefulness. It would be ideal to minimize such symptoms while not altering apraclonidine's ability to reduce intraocular pressure.

These symptoms could possibly be reduced by reformulation and reduction in drop size. Reformulation may allow greater adherence of the medication to the cornea, better corneal penetration, and less systemic absorption. This may allow for a comparable magnitude and duration of intraocular pressure reduction seen with the 1% solution, but with fewer side effects. A similar effect (a reduction in concentration from 0.5% to 0.25% with a comparable intraocular pressure reduction) has been seen with the reformulation of betaxolol hydrochloride.[9]

Previous studies with topical alpha-agonists[10] and beta-blockers[11] suggest that reducing the drop size affects intraocular pressure reduction minimally. The eyelid fornix normally holds less than 20 μl of solution.[12] A smaller eyedrop decreases the amount of medication reaching the eye and may allow for decreased eyelid pumping of the eyedrop and decreased systemic absorption. A smaller eyedrop may deliver a bigger effective dose because washout of medication through tearing would be minimal.

We evaluated the intraocular pressure reduction activity and systemic side effects of various eyedrop sizes, concentrations, and formulations of apraclonidine.

Subjects and Methods

We recruited 29 healthy volunteers who were 21 years of age or older. Subject mean age was 33 ± 10.1 years (range, 21 to 55 years). Five were men, 24 were women, 15 were black, and 14 were white. Subjects were excluded if they had any of the following: recent history of ocular trauma, infection, or inflammatory dis-

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ease; any abnormality preventing reliable tonometry; previous intraocular or laser operations; contact-lens wear during the study; monocular vision; unstable cardiopulmonary disease; chronic renal failure; received systemic alpha-agonists within 30 days before the study; or had a history of hypersensitivity to apraclonidine or clonidine. We also excluded women who were pregnant, nursing, or of childbearing potential. The hospital's investigational review board approved the study, and written informed consent was obtained from each subject.

We performed a double-masked, six-period crossover study in which subjects were randomly assigned to treatment using three controls, each with a 30-μl drop size (Table 1). The first was the vehicle of the commercially available 1% solution (placebo). The second was 1% apraclonidine solution. The third was a 30-μl solution of 0.5% apraclonidine with conventional formulation. We compared these to the three following different formulations of apraclonidine using a 16-μl drop size: a 0.5% solution of apraclonidine with hydroxypropylmethylcellulose added; a 0.5% solution of apraclonidine with both hydroxypropylmethylcellulose and the corneal penetration enhancer, lysolecithin, added; and a 16-μl 0.5% ophthalmic solution formulated identically to the commercially available 1% solution. Each subject randomly received all six medications with a one-week washout between periods.

On the first day of each crossover period we measured visual acuity, resting blood pressure, and heart rate, and performed slit-lamp biomicroscopy. We carefully placed only a single drop of study medication in both eyes of each subject. We examined the subjects one, three, eight, and 12 hours later. No topical anesthetic was given or intraocular pressure was measured before instillation of the study medication. This allowed us to evaluate better the efficacy of the corneal penetration enhancer, lysolecithin. Applanation tonometry can abrade the cornea, enhancing the penetration of a topical medication. Applanation tonometry before the administration of a glaucoma medication also does not mimic its use in a clinical situation. By instilling medication in subjects before applanation tonometry, there was no confusion between the effects of the penetration enhancer that we evaluated and the effects of topical anesthetic (proparacaine HCl) or its preservative (benzalkonium chloride) on the cornea.[13]

TABLE 1

DIFFERENCES IN FORMULATION AND DROP SIZE OF APRACLONIDINE MEDICATIONS FOR THE SIX STUDY ARMS

CONCENTRATION OF APRACLONIDINE	DROP SIZE (μL)	FORMULATION
None	30	Conventional
0.5%	30	Conventional
1%	30	Conventional
0.5%	16	Conventional
0.5%	16	Hydroxypropylmethylcellulose
0.5%	16	Hydroxypropylmethylcellulose with lysolecithin

At each subsequent interval, intraocular pressure was measured with Goldmann applanation tonometry. We also measured resting blood pressure and heart rate. Subjects estimated side effects and symptoms on an arbitrary scale from 0 to 9. Mild side effects were rated 1 to 3, moderate side effects were rated 4 to 6, and severe side effects were rated 7 to 9. These symptoms were subjective and we did not attempt to measure their severity objectively. The following symptoms were actively elicited: ocular burning, ocular stinging, ocular itching, ocular dryness, excessive tearing, blurred vision, dry mouth, bad taste in mouth, unusually dry nose, systemic tiredness, and systemic drowsiness.

After the 12-hour examination, we instilled a second drop of study medication in both eyes. Each subject was then given the bottles of study medication and asked to instill one drop in each eye twice daily over the next six days. Each subject was seen again one week later, 12 hours after the last eyedrop instillation. We again carefully instilled only one drop of the same study medication into both eyes of each individual. Subjects were examined at one, three, eight, and 12 hours later as on the first day. The identical sequence of examinations was repeated for the next study phase, after the washout.

We averaged the intraocular pressure readings from both eyes of each volunteer, treating each subject as a unit. Results were reported as mean ± 1 standard deviation. The Bonferroni paired *t*-test was used to evaluate data.

Results

Only one subject did not complete all study visits. This subject completed five of the six study phases and was eliminated during the final day of the last study phase because of an adverse reaction. No change in the visual acuity of any subject was found at any time during the study.

Baseline intraocular pressure was not measured on any study date. We used the placebo-treatment phase as a baseline value. This represented a normal diurnal curve for each subject. At each interval, we compared the results obtained for each study medication with those obtained during placebo treatment at the same interval (Table 2, Figure). All formulations of apraclonidine significantly reduced intraocular pressure, compared to placebo (P < .05). The maximal intraocular pressure reduction effect from placebo for all agents was observed at three hours (21.9% ± 16.6% to 26.0% ± 15.6%) and decreased to the range of 10% ± 19.6% to 16% ± 18.2% by 12 hours. Statistical analysis comparing each formulation to all other formulations showed no significant differences for any formulation. A similar intraocular pressure reduction was seen on Day 7 for all formulations. Comparison of intraocular pressure reduction efficacy of all formulations on Day 1 compared with Day 7 yielded no significant differences at all intervals.

The number of subjects whose intraocular pressure was reduced 20% by the placebo for all formulations was determined (Table 3). The 30-μl drop 0.5% apraclonidine solution with conventional formulation reduced intraocular pressure significantly more than the formulation containing both hydroxypropylmethylcellulose and lysolecithin on Day 7 at three hours. Although no other significant difference was observed, the 30-μl drop 0.5% apraclonidine with conventional formulation appeared to reduce intraocular pressure better than all other medications at this interval. No difference was found for any other formulations at any time point.

The percent change of mean systolic blood pressure ranged from −5.2% ± 10.4% to +5.0% ± 15.0% and the percent change of mean diastolic blood pressure ranged from −8.5% ± 12.3% to +5.8% ± 18.1%. No statistically significant differences (P < .05) were observed in the percent change from baseline value for systolic and diastolic blood pressure for any agent.

Data for the following side effects were not statistically different (nor did they approach significance) from placebo: burning, stinging, itching, tearing, dry nose, and bad taste. Data for side effects that were significantly different than those of the placebo were also determined (Tables 4 through 7). The formulation containing hydroxypropylmethylcellulose induced significantly more blurred vision than all other formulations (P = .004). The placebo induced significantly less (P < .05) dry mouth than apraclonidine 1% (P = .002), 16-μl 0.5% apraclonidine with conventional formulation (P = .032), and 30-μl 0.5% apraclonidine with conventional formulation (P = .032) but neither formulation with hydroxypropylmethylcellulose. Apraclonidine 1% induced significantly (P = .022) more dry mouth than both formulations with hydroxypropylmethylcellulose. Fatigue and drowsiness were more significant (P = .016) with apraclonidine 1% than with placebo. Tiredness was also less frequent (P = .04) with placebo when compared with the solution containing hydroxypropylmethylcel-

TABLE 2

MEAN INTRAOCULAR PRESSURE VALUES (± ONE STANDARD DEVIATION)

TIME	APRACLONIDINE WITH CONVENTIONAL FORMULATION			HYDROXYPROPYL-METHYLCELLULOSE	HYDROXYPROPYL-METHYLCELLULOSE WITH LYSOLECITHIN	PLACEBO
	30-μL 1.0%	16-μL 0.5%	30-μL 0.5%			
Day 1						
Hour 1	11.6 ± 2.6	12.4 ± 2.2	12.5 ± 2.8	12.9 ± 3.1	12.4 ± 2.7	14.7 ± 2.5
Hour 3	10.5 ± 2.5	10.9 ± 2.0	10.9 ± 2.4	10.9 ± 2.0	10.5 ± 2.1	14.3 ± 2.3
Hour 8	10.6 ± 2.8	11.7 ± 2.1	11.0 ± 1.9	11.2 ± 2.3	10.8 ± 2.1	13.3 ± 2.2
Hour 12	11.1 ± 2.2	11.7 ± 2.5	11.3 ± 2.6	11.9 ± 2.2	11.4 ± 2.4	13.5 ± 2.6
Day 7						
Hour 1	11.2 ± 2.4	12.5 ± 3.1	11.4 ± 2.8	11.6 ± 2.3	11.9 ± 2.9	14.4 ± 2.3
Hour 3	9.9 ± 2.1	11.1 ± 2.7	10.2 ± 2.5	10.7 ± 1.8	10.9 ± 2.5	13.7 ± 3.0
Hour 8	10.7 ± 2.7	11.8 ± 2.1	11.5 ± 2.2	11.7 ± 2.2	11.4 ± 2.8	13.3 ± 2.8
Hour 12	11.3 ± 2.5	12.0 ± 1.9	12.2 ± 2.3	11.8 ± 2.0	11.9 ± 2.3	13.7 ± 2.3

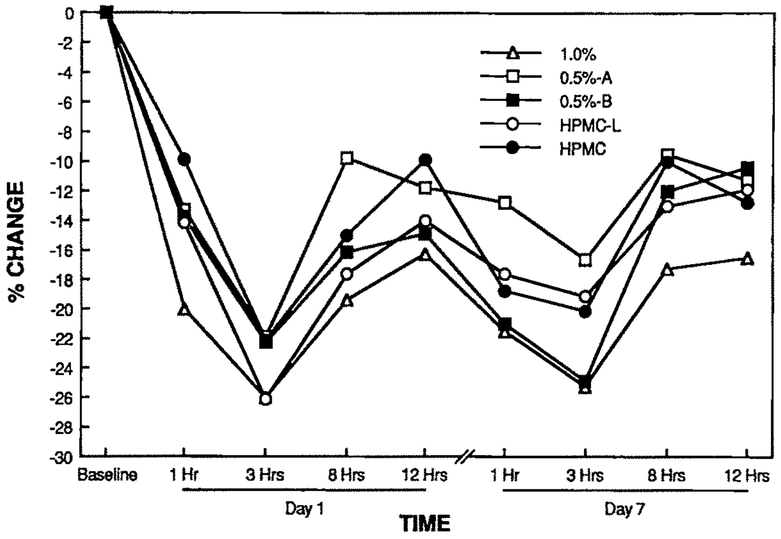

Figure (Vocci and associates). Line graph comparing the percent change in mean intraocular pressure from the placebo-treatment phase for all formulations and drop sizes. The open triangles represent the 30-µl eyedrop of the standard formulation of 1% apraclonidine. The solid squares represent 30-µl eyedrops of 0.5% apraclonidine with the standard formulation. The open squares represent standard formulation of 0.5% apraclonidine with a smaller 16-µl eyedrop size. Both the solid and open circles represent formulations of 0.5% apraclonidine using the smaller 16-µl eyedrop size. The solid circles represent formulations to which hydroxypropylmethylcellulose was added. The open circles represent the formulation to which lysolecithin was also added. No significant difference at any interval was observed between groups. No significant difference was observed in any group between mean percent intraocular pressure change from placebo at comparable times on Days 1 and 7. HPMC-L indicates hydroxypropylmethylcellulose and lysolecithin. HPMC indicates hydroxypropylmethylcellulose.

lulose and lysolecithin. Although the differences in drowsiness and tiredness between the 16-µl 0.5% apraclonidine with conventional formulation and apraclonidine 1% were not statistically significant at the $P \leq .05$ level, eight of the 29 subjects (27%) reported moderate to severe reactions with 1% apraclonidine compared to three of the subjects (10.5%) reporting the same level with the 16-µl 0.5% apraclonidine with conventional formulation. This trend might be significant if a larger sample size is used.

The one subject who was discontinued from the study reported the most severe side effect at Day 7 of her final study visit while receiving apraclonidine 1%. Before instillation of the medication on the last day of the study, this subject reported mildly blurred vision, burning, and photophobia. Slit-lamp biomicroscopy disclosed bilateral mild corneal punctate staining, mild conjunctival injection, and trace cell and flare in the anterior chamber. Two additional subjects receiving apraclonidine 1% had sparse corneal punctate staining but were asymptomatic. A mild headache was reported by two subjects receiving the 30-µl 0.5% apraclonidine with conventional formulation on Day 1. Nine subjects reported subjective mild blurring of vision after the instillation of both solutions containing hydroxypropylmethylcellulose. Five of these nine subjects reported that the blurring was transient, lasting less than one minute. Headache was reported by two subjects while using the formulation containing hydroxypropylmethylcellulose with lysolecithin.

Discussion

This study used a potentially commercially available eyedrop bottle that delivers a 16-µl drop size. Previous studies of other medications that used minidrops used either pipettes[10] or a prototype drop bottle.[11] We also evaluated multiple formulations and concentrations. Baseline intraocular pressure was not measured and the intraocular pressure data were analyzed as percent change from placebo. The data obtained from the placebo-treated group separated the pharmacologic effects of apraclonidine from diurnal variation and placebo effects.

TABLE 3
NUMBER OF SUBJECTS WITH A 20% REDUCTION IN INTRAOCULAR PRESSURE

TIME	APRACLONIDINE WITH CONVENTIONAL FORMULATION			HYDROXYPROPYLMETHYLCELLULOSE WITH LYSOLECITHIN	HYDROXYPROPYLMETHYLCELLULOSE
	30-μL 1.0%	16-μL 0.5%	30-μL 0.5%		
Day 1					
Hour 1	16	11	12	13	12
Hour 3	20	19	19	21	19
Hour 8	16	11	14	12	13
Hour 12	14	10	12	15	10
Day 7					
Hour 1	18	14	17	12	15
Hour 3	14	15	22*	13*	14
Hour 8	13	9	9	10	10
Hour 12	13	7	10	10	11

*30-μl 0.5% apraclonidine with conventional formulation significantly reduced intraocular pressure in more volunteers by 20% compared to hydroxypropylmethylcellulose with lysolecithin.

This method was important because statistically significant decreases in intraocular pressure have been observed in eyes in which placebo drops have been instilled.[7,14-16]

The data regarding the effect of the corneal penetration enhancer, lysolecithin, would have been confounded by the previous applanation of an anesthetized cornea had a baseline intraocular pressure been obtained. However, the main disadvantage of this study was that the data were calculated as a percent change from placebo rather than from baseline value. This may under- or overestimate the intraocular pressure-reducing ability of various formulations.

This study was conducted to determine whether reformulation or reduction in drop size, or both, of topically administered apraclonidine would affect its ocular hypotensive effects and its side effect profile. All formulations significantly reduced intraocular pressure compared to placebo. No significant differences in the average maximal intraocular pressure reduction were found for any formulation at any time point in the study compared to any other formulation. The maximal intraocular pressure-reducing effect was observed at three hours for all formulations. This was consistent with findings of previous studies.[6,7,17] The range of maximal response in this study varied from 21.9% ± 16.6% to 26.1% ± 15.6%. This range of maximal response was similar to previous apraclonidine studies,[7,17] which reported a 22.4% and 28.6% maximal response with 1% and 0.5% apraclonidine, respectively. Although our study used healthy adult volun-

TABLE 4
NUMBER OF SUBJECTS EXPERIENCING BLURRED VISION AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	29	0	0
Apraclonidine 1%	29	0	0
16-μl 0.5% apraclonidine with conventional formulation	29	0	0
30-μl 0.5% apraclonidine with conventional formulation	29	0	0
Hydroxypropylmethylcellulose with lysolecithin	24	5	0
Hydroxypropylmethylcellulose	20	6	3

TABLE 5
NUMBER OF SUBJECTS EXPERIENCING DRY MOUTH AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	29	0	0
Apraclonidine 1%	16	9	4
16-μl 0.5% apraclonidine with conventional formulation	23	4	2
30-μl 0.5% apraclonidine with conventional formulation	23	6	0
Hydroxypropylmethylcellulose with lysolecithin	25	2	2
Hydroxypropylmethylcellulose	25	3	1

TABLE 6
NUMBER OF SUBJECTS EXPERIENCING DROWSINESS AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	29	0	0
Apraclonidine 1%	23	2	4
16-μl 0.5% apraclonidine with conventional formulation	28	1	0
30-μl 0.5% apraclonidine with conventional formulation	27	1	1
Hydroxypropylmethylcellulose with lysolecithin	26	3	0
Hydroxypropylmethylcellulose	27	1	1

TABLE 7
NUMBER OF SUBJECTS EXPERIENCING TIREDNESS AS A SIDE EFFECT (N = 29)

	RATING OF SIDE EFFECT		
	NONE OR MILD	MODERATE	SEVERE
Placebo	28	1	0
Apraclonidine 1%	21	2	6
16-μl 0.5% apraclonidine with conventional formulation	26	2	1
30-μl 0.5% apraclonidine with conventional formulation	26	2	1
Hydroxypropylmethylcellulose with lysolecithin	21	7	1
Hydroxypropylmethylcellulose	25	3	1

teers, these results probably corresponded to potential short-term results seen in glaucomatous eyes as the results of our study were similar to those seen when topical apraclonidine was instilled in both healthy and glaucomatous eyes.[6]

The effective dose of all formulations of 0.5% apraclonidine with a reduced (16-μl) drop size is approximately one drop of a 0.25% solution. A previous dose-response study[7] that used concentrations of 0.125%, 0.25%, and 0.5% apraclonidine in subjects with ocular hypertension and glaucoma found no statistically significant differences between 0.25% and 0.5% solutions. The previous dose-response study[7] did find a difference in the percentage of patients with a greater than 20% reduction in intraocular pressure at eight hours for the 0.25% and 0.50% solutions. However, as in our present study, this difference did not attain significance with the exception of the formulation with hydroxypropylmethylcellulose and the conventional 30-μl 0.5% apraclonidine solution. Hydroxypropylmethylcellulose might lessen the effective concentration of apraclonidine.

The magnitude and duration of responses was similar for Day 1 and Day 7. The range of magnitude and duration of response was similar to that in previous studies using similar concentrations of apraclonidine.[7,17] This may indicate that short-term studies of apraclonidine could be as brief as 24 hours.

We detected no clinically or statistically significant differences in resting systolic or diastolic blood pressure or pulse rate in this study. Similar findings have been reported in several studies.[5,6,18]

The most commonly elicited side effects in our study were dry mouth, dry nose, fatigue, drowsiness, and burning on instillation. Fewer subjects reported side effects while taking 16-μl 0.5% apraclonidine with conventional formulation, the 30-μl 0.5% apraclonidine with conventional formulation, and both formulations containing hydroxypropylmethylcellulose when compared to apraclonidine 1% for fatigue, dry mouth, and bad taste. However, the decrease in side effects was not entirely dose-dependent. The trend was as might be expected; lower doses of apraclonidine were associated with a decrease in the number of subjects reporting complications, and the complications that were reported were milder. The only exception was transient blurring of vision induced by the formulations containing hydroxypropylmethylcellulose. This was subjective and visual acuity was not measured after the instillation of apraclonidine. This was most likely caused by the increased viscosity of hydroxypropylmethylcellulose. The addition of hydroxypropylmethylcellulose offered no apparent advantages, but had the disadvantage of blurred vision.

All subjects spontaneously volunteered information about the new (16-μl) eyedrop bottle. They agreed it was easier to squeeze and deliver one drop with this bottle and therefore preferred the new eyedrop bottle to the conventional eyedrop bottle.

Although the side effects were tolerable for the subject group as a whole, some of these side effects may limit the future applications of the drug in susceptible individuals. One subject developed mild ocular irritation and anterior chamber inflammation representative of an allergic reaction during the one-week instillation period with the apraclonidine 1% formulation. This reaction developed during the subject's sixth study phase and did not develop with any other formulation or drop size. This unusual reaction has been previously reported with 1% apraclonidine[17] and may represent a problem when used for long-term treatment of glaucoma. It is noteworthy that this reaction developed during the final phase (Week 6) of the study and may be related to the total duration of apraclonidine exposure.

This study demonstrated that reformulation or reduction in drop size, or both, is associated with a similar duration and magnitude of intraocular pressure reduction but can also be associated with a decrease in local and systemic side effects. Decreased eyelid pumping of a smaller drop volume contributed to the effects found in this study. These short-term results augur well for the future long-term instillation of apraclonidine hydrochloride as an ocular hypotensive agent in the management of glaucoma. Apraclonidine, when used in long-term treatment, may be most effective in a smaller drop size. A new long-term agent for the treatment of glaucoma must not only be safe and effective, but also have tolerable side effects. Apraclonidine in the form of the 0.5% solution with a 16-µl drop size was both effective and well-tolerated.

References

1. Robin, A. L., Pollack, I. P., House, B., and Enger, C.: Effects of ALO 2145 on intraocular pressure following argon laser trabeculoplasty. Arch. Ophthalmol. 105:646, 1987.
2. Robin, A. L., Pollack, I. P., and deFaller, J. M.: Effects of topical ALO 2145 (p-aminoclonidine hydrochloride) on the acute intraocular pressure rise following argon laser iridotomy. Arch. Ophthalmol. 105:1208, 1987.
3. Brown, R. H., Stewart, R. H., Lynch, M. G., Crandell, A. S., Mandell, A. I., Wilensky, W. T., Schwartz, A. L., Gaasterland, D. E., deFaller, J. M., and Higginbotham, E. J.: ALO 2145 reduces the intraocular pressure elevation after anterior segment laser surgery. Ophthalmology 95:378, 1988.
4. Robin, A. L.: The role of apraclonidine hydrochloride in laser therapy for glaucoma. Trans. Am. Ophthalmol. Soc. 87:729, 1989.
5. Abrams, D. A., Robin, A. L., Pollack, I. P., deFaller, J. M., and DeSantis, L.: The safety and efficacy of topical 1% ALO 2145 (p-aminoclonidine hydrochloride) in normal patients. Arch. Ophthalmol. 105:1205, 1987.
6. Abrams, D. A., Robin, A. L., Crandall, A. S., Caldwell, D. R., Schnitzer, D. B., Pollack, I. P., Rader, J. E., and Reaves, T. A.: A limited comparison of apraclonidine's dose response in subjects with normal or increased intraocular pressure. Am. J. Ophthalmol. 106:230, 1989.
7. Jampel, H. D., Robin, A. L., Quigley, H. A., and Pollack, I. P.: Apraclonidine. A one week dose response study. Arch. Ophthalmol. 106:1069, 1988.
8. Morrison, J. C., and Robin, A. L.: Adjunctive glaucoma therapies. A comparison of apraclonidine and dipivefrin when added to timolol maleate. Ophthalmology 96:3, 1989.
9. Weinreb, R. N., Caldwell, D. R., Goode, S. M., Horwitz, B. L., Laibovitz, R., Shrader, C. E., Stewart, R. H., and Williams, A. T.: A double-masked three month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution. Am. J. Ophthalmol. 110:189, 1990.
10. Petursson, G., Cole, R., and Hanna, C.: Treatment of glaucoma using minidrops of clonidine. Arch. Ophthalmol. 102:1180, 1984.
11. Brown, R. H., and Lynch, M. G.: Design of eyedropper tips for topical beta-blocking agents. Am. J. Ophthalmol. 102:123, 1986.
12. Holly, F. J., and Lemp, M. A.: Wettability and wetting of corneal epithelium. Exp. Eye Res. 11:239, 1971.
13. Camber, O., and Edman, P.: Influence of some preservatives on the corneal permeability of pilocarpine and dexamethasone. Int. J. Pharmacol. 39:229, 1984.
14. Caldwell, J. R., Salisbury, G. R., and Guzek, J. P.: Effect of topical betaxolol on ocular hypertensive patients. Arch. Ophthalmol. 102:539, 1984.
15. Partamian, L. G., Kass, M. A., and Gordon, M.: A dose response study on the effect of levobunolol on ocular hypertension. Am. J. Ophthalmol. 95:229, 1983.
16. Zimmerman, T. J., and Kaufman, H. E.: Timolol. Dose response and duration of action. Arch. Ophthalmol. 95:605, 1979.
17. Robin, A. L.: Short-term effects of 1% apraclonidine therapy. Arch. Ophthalmol. 106:912, 1988.
18. Hernandez, Y., Hernandez, H., Cervantes, R., Frati, A., Hurtado, R., McDonald, T. O., and DeSousa, B.: Cardiovascular effects of topical glaucoma therapies in normal subjects. J. Toxic Cut. Ocular Toxicol. 2:99, 1983.

Preserved Para-arteriolar Retinal Pigment Epithelium Retinitis Pigmentosa

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In two patients, we studied retinitis pigmentosa with preservation of the retinal pigment epithelium adjacent to and under the retinal arterioles (despite panretinal degeneration). Both patients with preserved para-arteriolar retinal pigment epithelium also exhibited a peculiarly strong hyperopia. In addition to previously reported features, these patients also had sheathing of the major vascular arcades, which suggested a vascular involvement in this uncommon form of retinitis pigmentosa.

RETINITIS PIGMENTOSA, as well as other retinal and choroidal diseases, may be classified in various ways.[1] Inheritance patterns and fundus features are correlated with results of electrophysiologic and psychophysical tests such as electroretinography, electro-oculography, a dark adaptation test, and measurement of the visual field. Many retinal dystrophies have also been classified according to the appearance of the fundus, and its unusual forms of retinitis pigmentosa have been reported as pigmented paravenous retinochoroidal atrophy,[2] sector retinitis pigmentosa,[3] retinitis punctata albescens,[4] and retinitis pigmentosa sine pigmento.[5] The inheritance of a fundus pattern with the same features and clinical symptoms strongly suggests a single-gene disease. Heckenlively[6] described a few hyperopic patients with advanced retinitis pigmentosa and para-arteriolar preservation of the retinal pigment epithelium and designated this disease as preserved para-arteriolar retinal pigment epithelium retinitis pigmentosa. Recently, more than 300 patients with retinitis pigmentosa have been referred to our institution, which is the Reference Center in Lombardy (northern Italy) for the Italian Retinitis Pigmentosa Association. We have identified two patients with uncommon forms of retinitis pigmentosa and with clinical and structural features resembling Heckenlively's definition of preserved para-arteriolar retinal pigment epithelium retinitis pigmentosa. However, unlike Heckenlively, we found a diffuse sheeting of major retinal vessels in our first patient and macular edema in the second.

Case Reports

Case 1

A 19-year-old woman had poor visual acuity and night blindness since the age of 3 years. She complained of a sudden worsening in visual acuity at the age of 13 years that coincided with the beginning of menstruation. Family history disclosed no other relative with retinitis pigmentosa or any other eye problem. Consanguinity was eliminated. On examination, the patient had a visual acuity of 20/200 with a correction of +9.00 +2.00 × 100 in each eye. Slit-lamp examination disclosed slight posterior subcapsular opacities in both eyes. Full-field electroretinography, performed according to the International Standardization Committee protocol,[7] was unrecordable. Goldmann perimetry with the IV_{4e} isopter disclosed a central field of less than 10 degrees, with small islands 20 degrees from the fixation point. Ophthalmoscopy disclosed macular atrophy in both eyes with yellow-white deposits and isolated pigmentary clumps in the posterior pole. The retinal periphery appeared atrophic with scattered bone spicule pigments. Diffuse sheathing

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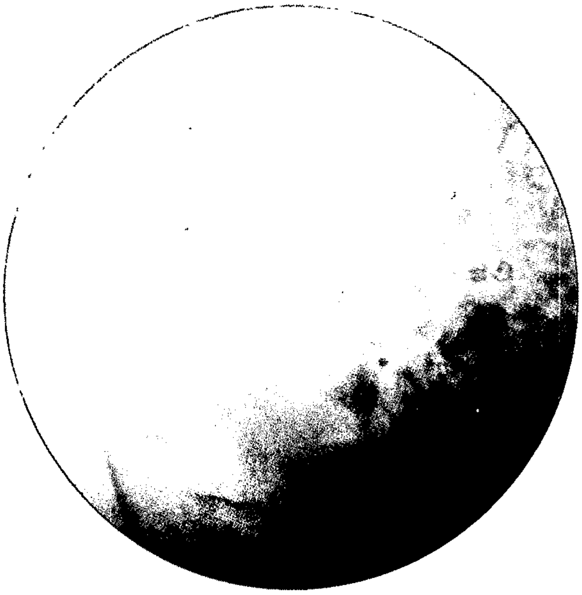

Fig. 1 (Porta and associates). Case 1. Fundus photograph of preserved para-arteriolar retinal pigment epithelium retinitis pigmentosa shows macular atrophy with yellow-white deposits and isolated pigmentary clumps in the posterior pole and diffuse sheathing of major retinal vessels.

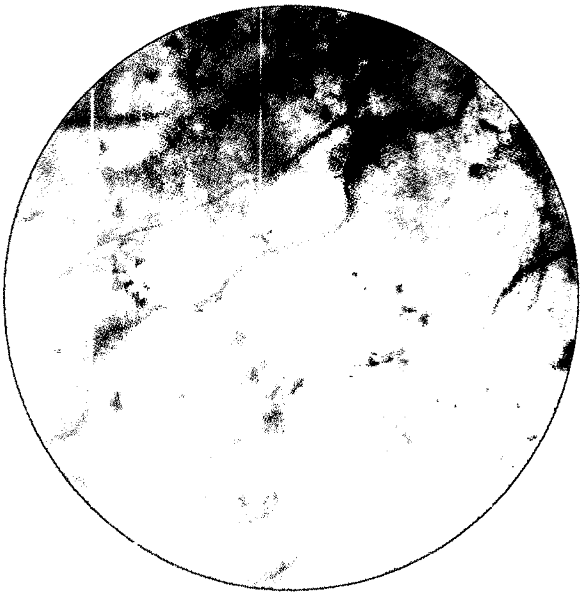

Fig. 2 (Porta and associates). Case 1. Fundus photograph shows preservation of the retinal pigment epithelium adjacent to and under the retinal arterioles.

of major retinal vessels was also observed (Fig. 1). In the midperiphery and periphery, preservation of the retinal pigment epithelium adjacent to and under the retinal arterioles could be seen (Fig. 2). Fluorescein angiography confirmed the periarteriolar preservation of the retinal pigment epithelium in the localized region of the fundus, whereas in other areas, the retinal pigment epithelium was missing next to the arterioles (Fig. 3). Staining of the vessel walls was also observed to correspond to the sheeting of the major arterial and venous trunk. Marked retinal edema was apparent in the advanced phases of angiography along the vascular arcades and in the peripapillary area (Fig. 4).

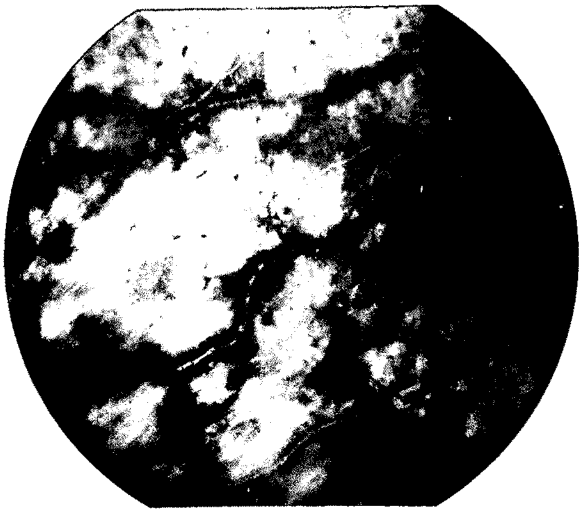

Fig. 3 (Porta and associates). Case 1. The preserved para-arteriolar retinal pigment epithelium pattern shown in Figure 2 was confirmed by fluorescein angiography.

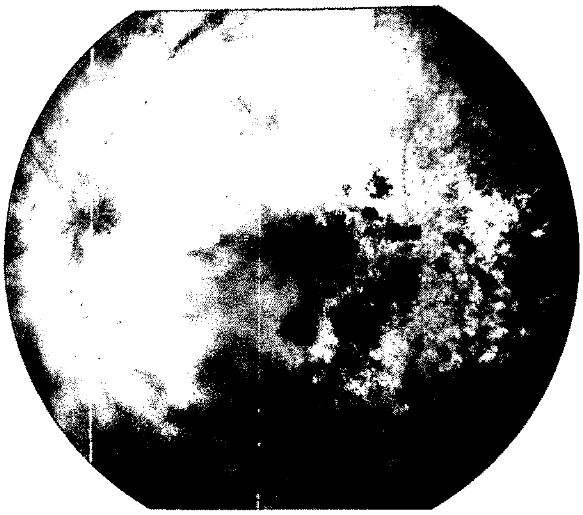

Fig. 4 (Porta and associates). Case 1. Marked retinal edema was apparent in the advanced phases of angiography along the vascular arcades and in the peripapillary area.

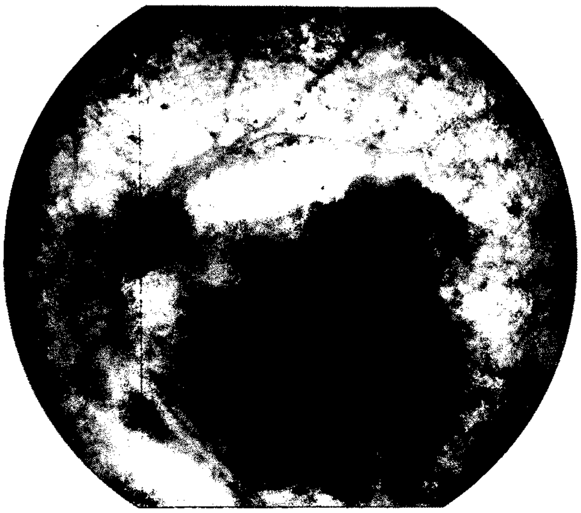

Fig. 5 (Porta and associates). Case 2. Fluorescein angiogram shows preserved para-arteriolar retinal pigment epithelium retinitis pigmentosa and macular edema.

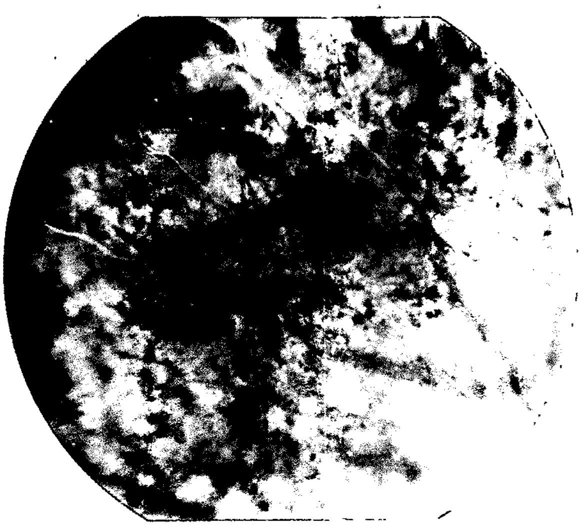

Fig. 6 (Porta and associates). Case 2. Fluorescein angiogram demonstrate preservation of the retinal pigment epithelium in a para-arteriolar distribution.

The patient's 22- and 17-year-old sisters were also examined. The elder sister's refraction was R.E.: −1.50 and L.E.: −3.75; and the younger sister's refraction was both eyes: −3.75. Both sisters had a visual acuity of 20/20. Results of Goldmann perimetry, scotopic and photopic electroretinography, and ophthalmoscopy were normal.

Case 2

A 7-year-old girl had poor visual acuity and night blindness since the age of 1 year. No family history of eye problems or consanguinity was found. At slit-lamp examination, the anterior segment of the eye was normal. Visual acuity was R.E.: 20/50, with a correction of +2.00 +2.00 × 90 and L.E.: 20/70, with +2.00 +2.50 × 90. Goldmann visual field perimetry showed central 10 degrees preservation with concentric isopters resembling onions. Full-field electroretinography was barely recordable. Fundus examination disclosed mildly attenuated retinal vessels, diffuse atrophy in the far and midperiphery, and sparse pigment clumping, but no bone spicule pigmentation in both eyes. The maculas had retinal pigment epithelium defects. Preservation of the retinal pigment epithelium could be seen adjacent to and under the retinal arterioles in all quadrants of both eyes in the far and midperiphery. Fluorescein angiography showed pigment epithelial transmission defects in the far and midperiphery and macular edema was also evident (Fig. 5). The preservation of retinal pigment epithelium in a para-arteriolar distribution was more evident on fluorescein angiography (Fig. 6). We also examined the two brothers and the sister of this patient. Results were normal for all of them, although one boy had medullated nerve fiber of the optic nerve head at initial fundus examination.

Discussion

The main argument supporting the identification of our two cases with the preserved para-arteriolar retinal pigment epithelium retinal dystrophy as described by Heckenlively is the perivascular pigment epithelium pattern.[6] However, there are many other common features between our cases and those previously reported. On fundus examination, we found yellow-white deposits in the posterior pole in one patient, and pigment clumps and mildly attenuated retinal vessels in both. Unlike in the previously described cases, we did not find drusen or other optic nerve head abnormalities, our two pedigrees suggested an autosomal recessive inheritance, and our patients were also hyperopic.

Hyperopia is uncommon in patients with retinitis pigmentosa, which is usually more closely associated with myopia.[8,9] It is possible that the axial hyperopia may have represented a genetically associated trait or that degeneration of the retina and retinal pigment epithelium may have influenced the developmental growth of the globe in some way. Preserved para-arteriolar retinal pigment epithelium retinitis pigmentosa, like Leber's congenital amaurosis, which is also associated with marked hyperopia, manifests itself in childhood, and is more severe than retinitis pigmentosa.

The perivascular preservation of the retinal pigment epithelium was particularly evident on fluorescein angiography; we therefore consider this examination necessary for confirming the diagnosis of preserved para-arteriolar retinal pigment epithelium. The preservation of the retinal pigment epithelium adjacent to arterioles despite a panretinal degenerative process could imply some positive interaction between the retinal pigment epithelium and the arterioles. An oxygenation effect from the arterioles (but the retinal pigment epithelium does not derive its nutrition from the retinal circulation and some pigment preservation may also be seen near the veins) or a reduction in light exposure caused by the shadow of the overlying vessels (but the same pattern does not appear under and adjacent to the major retinal vessels) was assumed to explain the preserved para-arteriolar retinal pigment epithelium pattern. It has also been suggested that a permeable factor, released by the retinal arterioles, may help to preserve the retinal pigment epithelium by delaying the degeneration process.[6]

Sheathing of the vascular wall was not observed in the cases reported by Heckenlively.[6] In our cases it was limited to the large retinal vessels (that is, thosewithout preserved retinal pigment epithelium) and may have indicated vascular involvement, which was also demonstrated by the extensive retinal edema in the first case. Because our cases were the only ones found in a series of 300 consecutive cases of pigmentary retinal degenerations referred to our institution, the extreme infrequency of this disease is substantially confirmed.

References

1. Marmor, M. F., Aguirre, G., Arden, G., and 25 other authors: Retinitis pigmentosa. A symposium on terminology and methods of examination. Ophthalmology 90:126, 1983.
2. Pearlman, J. T., Kamin, D. F., Kopelow, S. M., and Saxton, J.: Pigmented paravenous retinochoroidal atrophy. Am. J. Ophthalmol. 80:630, 1975.
3. Krill, A. E., Archer, D., and Martin, D.: Sector retinitis pigmentosa. Am. J. Ophthalmol. 69:977, 1970.
4. Krill, A. E.: Hereditary Retinal and Choroidal Diseases. Clinical Characteristics, vol. 2. Hagerstown, Harper & Row, 1977, 2:500, pp. 747–748.
5. Pearlman, J. T., Flood, T. P., and Seiff, S. R.: Retinitis pigmentosa without pigment. Am. J. Ophthalmol. 81:417, 1976.
6. Heckenlively, J. R.: Preserved para-arteriole retinal pigment epithelium (PPRPE) in retinitis pigmentosa. Br. J. Ophthalmol. 66:26, 1982.
7. International Standardization Committee: Standard for clinical electroretinography. Arch. Ophthalmol. 107:816, 1989.
8. Foxman, S. G., Heckenlively, J. R., and Bateman, J. B.: Classification of congenital and early onset retinitis pigmentosa. Arch. Ophthalmol. 103:1502, 1985.
9. Laties, A. M., and Stone, R. A.: Ametropia in retinal disorders. In Anderson, R. E., Hollyfield, J. G., and La Vail, M. M. (eds.): Proceedings of the Stockholm Symposium on Retinal Degenerations, Boston, CRC Press, 1990, p. 383.

Abnormal Rod Dark Adaptation in Autosomal Dominant Retinitis Pigmentosa With Proline-23-Histidine Rhodopsin Mutation

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We studied rod and cone function in 13 patients from four families with autosomal dominant retinitis pigmentosa and the proline-23-histidine rhodopsin mutation. In patients with early stages of this disease, rod sensitivity was mildly abnormal throughout the retina and cone sensitivity was normal. In more severely affected patients, sensitivity loss varied with retinal region, some regions showing mild rod loss only and other regions having pronounced rod and cone dysfunction. Rhodopsin levels were decreased below normal by amounts that indicated the rod sensitivity loss was determined by the reduced ability to absorb light. The most characteristic abnormality of this genotype was a slowed rod branch of dark adaptation, which was present regardless of the extent or severity of disease. The time required for recovery of rod sensitivity was more than twice the normal time. These findings with dark-adapted perimetry, fundus reflectometry, and dark adaptometry showed intrafamilial and interfamilial consistency.

Many point mutations in the gene encoding rhodopsin have been shown to correlate with retinal degeneration in autosomal dominant retinitis pigmentosa.[1-14] Of these, the transversion mutation in codon 23 of rhodopsin is the most frequently encountered in the United States, where it accounts for approximately 12% of the population of patients with autosomal dominant retinitis pigmentosa[2] and 62% of those in whom a rhodopsin mutation has been established.[5] Clinical assessments using ocular examinations and traditional tests of visual function in patients with the proline-23-histidine (P23H) rhodopsin mutation have reported substantial heterogeneity with respect to age of onset and severity of the disease.[9,12] We were therefore interested in determining whether more detailed testing would lead to any pattern of ocular findings common to all patients with this mutation.

We studied 13 patients representing four families with the P23H mutation. In this study we used electroretinography, kinetic perimetry, light- and dark-adapted static perimetry, dark adaptometry, and fundus reflectometry to test visual function. Our results using electroretinography and kinetic perimetry confirmed the apparent variability reported to be associated with this mutation,[9,12] but we found intrafamilial and interfamilial consistency in the patterns of rod and cone dysfunction with static perimetry and a characteristic abnormality of rod dark adaptation in all the patients tested, regardless of the extent or severity of their disease. Abnormally prolonged rod dark adaptation has also been reported previously[11] in patients with autosomal dominant retinitis pigmentosa with two other rhodopsin mutations (threonine-58-arginine [T58R] and threonine-17-methionine [T17M]) and in others of unknown genotype.[15-17] Our present results sug-

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gest the characteristics of the abnormality in patients with the P23H mutation differ quantitatively from those with T58R and T17M mutations.

Patients and Methods

Thirteen patients from four families with autosomal dominant retinitis pigmentosa were included in this study. The patients were known to have the rhodopsin P23H gene mutation on the basis of results of molecular genetic investigation.[5] All patients underwent clinical ocular examinations, traditional tests of visual function (Goldmann kinetic perimetry and full-field rod and cone electroretinography), and dark- and light-adapted static threshold perimetry. Subsets of patients were further studied with dark adaptometry and imaging fundus reflectometry. Informed consent was given by all subjects after a full explanation of the procedures was provided.

Goldmann kinetic perimetry was performed in both eyes of all patients using targets V (64 mm^2 area) and I (0.25 mm^2 area) at intensity 4e (318 cd/m^2) on a 10-cd/m^2 white background; the visual field extent was quantified by a published method.[18,19] Full-field rod and cone electroretinography was performed in one eye of all patients using previously described methods.[18,20]

Static threshold perimetry was performed in one eye of all patients using monochromatic stimuli (target area, 64 mm^2) in the dark- and light-adapted states. Dark-adapted perimetry was performed with 650- and 500-nm targets and light-adapted (10 cd/m^2) perimetry with a 600-nm target. Details of the technique, analysis methods, and normal results have been published.[19-22] The following two test strategies were used: a full-field test of 75 loci (12-degree grid) and a horizontal profile test (at 2-degree spacing) in the central 60 degrees. For the dark-adapted testing, the sensitivity difference between the 500- and 650-nm stimuli at each test location determines if rods, cones, or both are mediating detection of the stimulus.[21-23] Sensitivity losses were calculated for rods (on the basis of 500-nm test results, dark-adapted) and for cones (on the basis of 600-nm test results, light-adapted) by comparison to normal mean values.[19]

Dark adaptometry was performed at 12 degrees inferior, or at a location as close to that as possible in patients with gross impairment of rod function at 12 degrees. Testing was performed with 460- or 500- and 650-nm stimuli (target area, 64 mm^2) using previously reported methods.[11] The yellow bleaching light, which was of intensity 5.75 log scotopic trolands and a duration of one minute (expected to bleach approximately 95% of the rhodopsin in the region of the retina exposed to the light in the normal eye[24]), was delivered with Maxwellian optics, using a Zeiss fundus camera. The 30-degree diameter region exposed to the bleaching light was centered on the retinal location to be tested, using ipsilateral fixation. Baseline dark-adapted (more than three hours) thresholds were established at or before the beginning of the adaptometry sessions, at times when there had been no exposure to bright lights for at least 16 hours.[15]

Imaging fundus reflectometry was performed with instrumentation and procedures already described.[11,25-27] Images of the retina were obtained using a high-sensitivity television system attached to a Zeiss fundus camera. The retina was illuminated with a sequence of eight dim monochromatic measuring lights (ranging from 460 to 680 nm). The luminance levels of the retinal images of the fully light-adapted eye were compared to those obtained when the eye had been in the fully dark-adapted state. The spectral variation of the density changes (the differences of the logarithms of the reflectance values obtained for the two conditions) provides a measure of the level of visual pigment in dark-adapted retinas. In the procedure, the subject (with fully dilated pupil) was aligned with the instrument using the minimal amount of light, which was restricted to wavelengths greater than 560 nm. The test area was usually centered at 12 degrees in the superior retina. Fundus reflectometric images were recorded, and the subject was then light-adapted with a yellow light of intensity 5.75 log scotopic trolands delivered for a period of one minute to an area of retina concentric with, but larger than, the test area. This light exposure was expected to have removed more than 95% of the rhodopsin originally present.[24,25] Images of the test area of the retina were collected after the end of this exposure. Rhodopsin losses for the patients were determined by comparing their double density difference values (at 520 nm) with those from matched retinal locations in normal subjects.

Two-color, dark-adapted static perimetric measurements were also made at 25 locations

TABLE

CLINICAL CHARACTERISTICS OF PATIENTS WITH AUTOSOMAL DOMINANT RETINITIS PIGMENTOSA AND THE PROLINE-23-HISTIDINE RHODOPSIN MUTATION

PATIENT NO., FAMILY NO., AGE (YRS), GENDER	EYE	VISUAL ACUITY	KINETIC VISUAL FIELD EXTENT (%)[*]		ROD[†] ELECTRORETINOGRAM		MIXED CONE-ROD[‡] ELECTRORETINOGRAM		CONE[§] ELECTRORETINOGRAM	
			V_{4e}	I_{4e}	AMPLITUDE (μV)	TIMING (MS)	AMPLITUDE (μV)	TIMING (MS)	AMPLITUDE (μV)	TIMING (MS)
1, 1, 18, F	R.E.	20/20	100	100	86	104	219	52	116	30
	L.E.	20/20	100	100						
2, 1, 39, F	R.E.	20/60[‖]	26	< 1	ND	—	31	60	6	45
	L.E.	20/70[‖]	27	< 1						
3, 1, 62, F	R.E.	20/30[‖]	28	4	ND	—	22	62	3	46
	L.E.	20/40[‖]	35	3						
4, 2, 19, F	R.E.	20/20	99	16	ND	—	NA	—	23	39
	L.E.	20/20	98	8						
5, 2, 22, F	R.E.	20/20	100	100	80	100	266	61	70	28
	L.E.	20/20	100	100						
6, 2, 33, F	R.E.	20/25	87	3						
	L.E.	20/20	93	8	13	119	43	64	19	43
7, 2, 54, M	R.E.	20/20	95	6						
	L.E.	20/20	100	7	ND	—	43	64	20	44
8, 2, 78, M	R.E.	20/25[‖]	100	30	ND	—	47	70	23	47
	L.E.	20/25[‖]	92	25						
9, 3, 28, M	R.E.	20/20	43	15	ND	—	50	66	14	42
	L.E.	20/20	48	21						
10, 3, 31, M	R.E.	20/20	83	5						
	L.E.	20/40	77	3	ND	—	ND	—	ND	—
11, 3, 32, F	R.E.	20/20	44	13						
	L.E.	20/20	43	11	ND	—	94	67	16	39
12, 3, 59, F	R.E.	3/200[¶]	1	—	ND	—	ND	—	ND	—
	L.E.	20/30[¶]	1	< 1						
13, 4, 53, F	R.E.	20/40[‖]	16	2	ND	—	ND	—	ND	—
	L.E.	20/40[‖]	16	2						

[*] Expressed as a percent of normal mean; 2 standard deviations below normal equals 90% for V_{4e} and 88% for I_{4e}.

[†] Normal amplitude mean equals 299 μV, S.D. equals 52 μV; normal timing mean equals 76 ms, S.D. equals 5 ms.

[‡] Normal amplitude mean equals 497 μV, S.D. equals 111 μV; normal timing mean equals 48 ms, S.D. equals 6.5 ms.

[§] Normal amplitude mean equals 98 μV, S.D. equals 24 μV; normal timing mean equals 27 ms, S.D. equals 1.0 ms.

[‖] Cataract.

[¶] Aphakia or pseudophakia.

ND indicates not detectable; NA indicates not available.

on a rectangular grid covering an area of retina of 30 × 30 degrees. The test region was centered on the same retinal area as that where rhodopsin was measured, and the data were obtained before the retina was exposed to fundus reflectometric light adaptation.[11]

Results

The 13 patients we examined with retinal function tests are numbered on the pedigrees (Fig. 1) and these numbers correspond to the case numbers in the Table.

Almost all of the patients had good visual acuity (Table). Eight had 20/20 in one or both eyes and another four had between 20/25 and 20/40 in their better eye or in both eyes. Kinetic visual field extent and pattern of loss varied within and between families. In Family 1, Patient 1 had a normal visual field extent with both target sizes; her mother's visual field (Patient 2) was reduced to central and peripheral temporal islands only; and the grandmother's visual field (Patient 3) showed an altitudinal pattern of loss with almost all residual function located in the inferior field. All five members of Family 2 (Patients 4 through 8) had normal or nearly normal extents of their visual fields with

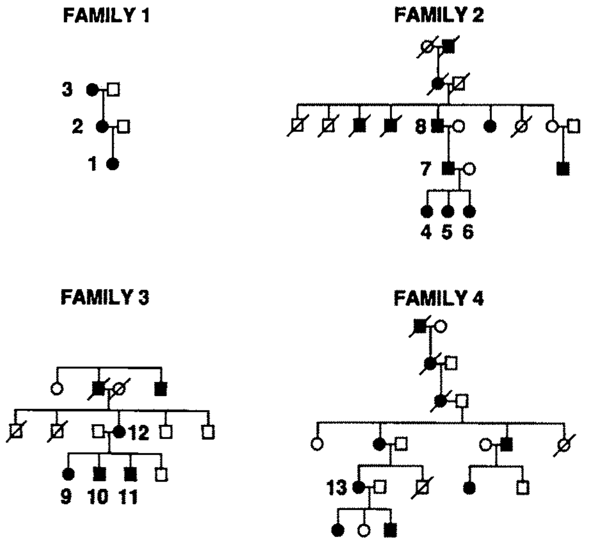

Fig. 1 (Kemp and associates). Pedigrees of the four families with autosomal dominant retinitis pigmentosa in this study. Filled symbols are affected family members and unfilled symbols are unaffected members; slashed symbols are deceased members. The patients examined are numbered to correspond with the case numbers in the Table.

the larger target, but only Patient 5 had a normal extent with the small target also. In Patients 4 and 8, the pattern of loss with the smaller target suggested greater dysfunction in the superior than in the inferior field; Patient 6 had greater inferior than superior field dysfunction; and Patient 7 had superior and inferior midperipheral dysfunction. Two siblings in Family 3 (Patients 9 and 11) showed greater superior than inferior field loss but a third sibling (Patient 10) did not; the visual field of their mother (Patient 12) was reduced to only a small central island. Patient 13 had islands only in the central and peripheral temporal field. On ophthalmoscopy, Patients 1 and 5 had normal-appearing fundi, whereas all others showed varying degrees of retinal vessel attenuation and pigmentary change. The patients with altitudinal visual field loss tended to show more pigmentary abnormalities in retinal regions corresponding to those with greater degrees of dysfunction.

All 13 patients had abnormal or undetectable rod and mixed cone-rod electroretinograms (Table). Only Patient 5 had a cone-flicker electroretinogram that was normal in amplitude and timing; the other four members of Family 2 showed reduced amplitudes and delayed timing for this signal. The cone-flicker electroretinogram of Patient 1 was normal in amplitude but slightly delayed in timing and the other two members of Family 1 showed markedly reduced amplitudes and prolonged timing. Two members of Family 3 (Patients 10 and 12) and Patient 13 had no detectable rod or cone signals, despite computer averaging.

The types of abnormalities in kinetic visual fields and rod and cone sensitivities found in this study are exemplified with data from three patients (Patients 1, 4, and 9; Fig. 2). Patient 1 was the most mildly affected and had kinetic fields within normal limits. Dark-adapted two-color static perimetry indicated that all extrafoveal test loci in this patient were rod-mediated or mixed rod- and cone-mediated. Rod sensitivity was abnormally reduced (> 2 standard deviations from the mean normal at each test locus) at most of the loci. Similar results were obtained from Patient 5, who was also mildly affected. Mean rod sensitivity losses were 9 dB (standard deviation, 3.8 dB) in Patient 1 and 9.5 dB (standard deviation, 2.5 dB) in Patient 5. Cone sensitivity was within 2 standard deviations of the normal mean at all loci in Patient 1 and at all but four loci (each with approximately 5-dB loss) in Patient 5. Rod sensitivity losses therefore can be detected at a time when cone sensitivity losses are not.

More severe abnormalities are exemplified in the kinetic perimetry and dark- and light-adapted static threshold perimetry results of Patients 4 and 9 (Fig. 2). Patient 4 had a normal extent of kinetic field with the V_{4e} target but had only a central island with an extension into the inferior and nasal field and a small superonasal island with the I_{4e} target. Patient 9 had an absolute scotoma occupying most of the superior field; the island with the I_{4e} target extended mainly from the central field into the inferior and nasal field. With static threshold perimetry, both patients showed regions of severe rod sensitivity losses and other regions with less rod dysfunction. The gray-scale maps show a relationship between degrees of rod and cone sensitivity losses. The more pronounced the rod sensitivity loss in an area of visual field, the greater the cone sensitivity loss therein. Regions of less severe rod dysfunction showed little or no cone dysfunction. This relationship of rod to cone sensitivity loss in the static threshold perimetric results of Figure 2 was also evident in all other patients in this study who had sufficient rod and cone function to permit such a comparison.

Two-color dark-adapted profiles along the

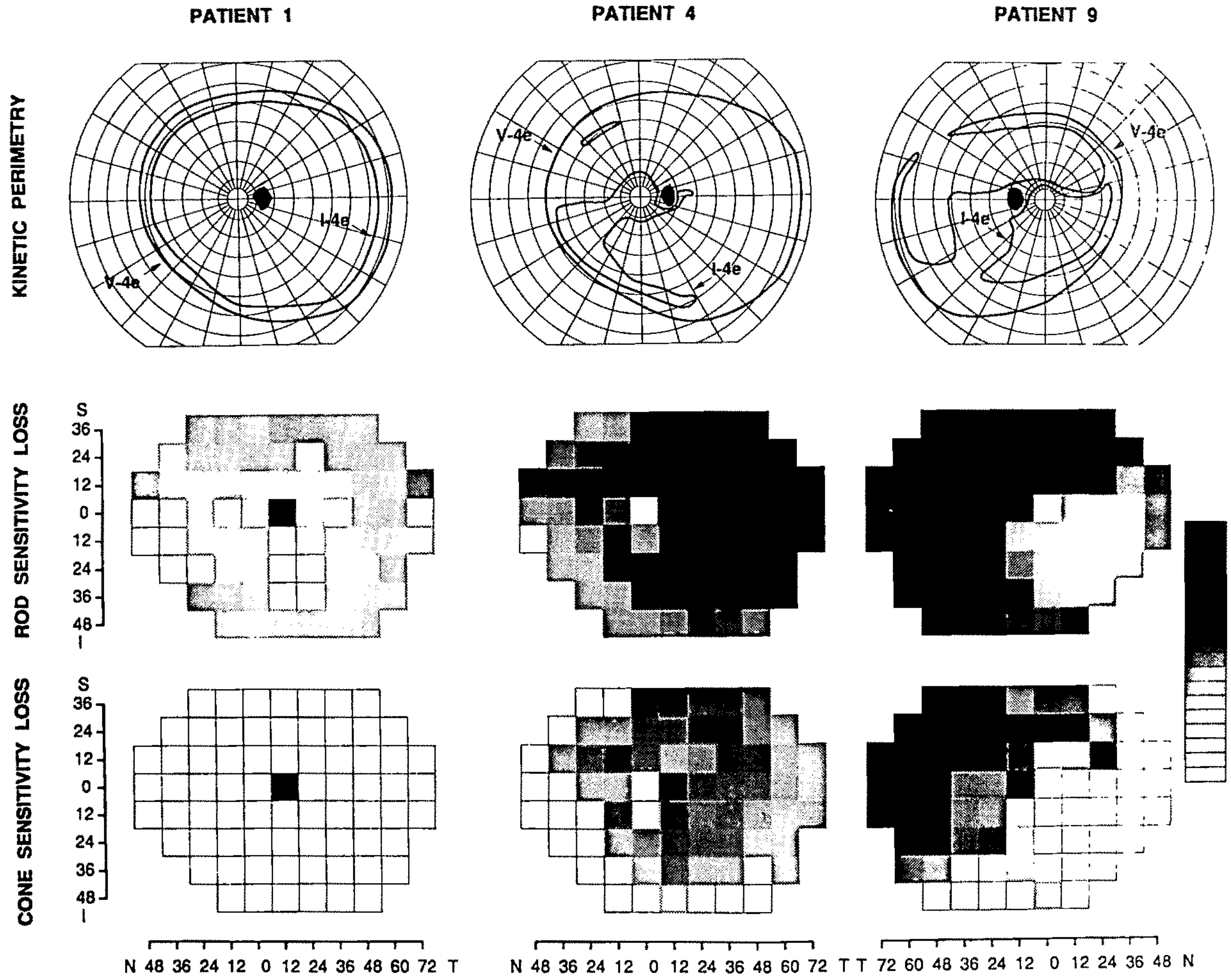

Fig. 2 (Kemp and associates). Top, Kinetic perimetry; middle, dark-adapted static threshold perimetry; and bottom, light-adapted static threshold perimetry in the right eyes of Patient 1 (left) and 4 (middle), and the left eye of Patient 9 (right). Results of static perimetry are displayed as gray scales of rod and cone sensitivity losses. Gray scales have 16 levels of gray, ranging from 0 to 54 dB for rods and 0 to 30 dB for cones. Black indicates no detection of the stimulus. White indicates test result was within 2 standard deviations of the mean normal sensitivity for that locus.

horizontal meridian in patients representing three generations each from two families are shown in Figure 3. Patient 1 of Family 1 showed mixed rod and cone mediation (500 nm detected by rods and 650 nm by cones; sensitivity difference between 13 and 27 dB[21,22]) within the central 20 degrees, but rod photoreceptor mediation (both colors detected by the rod system; sensitivity difference between colors, ≥ 28 dB[21,22]) at greater eccentricities. These rod sensitivities to the 500-nm stimulus at many of the loci were just within 2 standard deviations of the normal mean, whereas at other loci they were just outside the normal limits. A more advanced stage of dysfunction was seen in the data of the grandmother, Patient 3. Rod sensitivity was within normal limits at a few paracentral mixed-mediated loci, but sensitivity loss increased with eccentricity and no function was measurable to the 500-nm stimulus beyond approximately 15 degrees. Patient 2, the mother of Patient 1 and daughter of Patient 3, showed an even more advanced stage with no measurable rod function in the central 60 degrees. Only a cone-mediated (both colors detected by the cone system; sensitivity difference was ≤ 12 dB[21,22]) central island was present and cone sensitivity was reduced more than 2 standard deviations from the mean normal (determined during the cone plateau of dark adaptation) at all the loci.

Patient 5 of Family 2 (Fig. 3) resembled Pa-

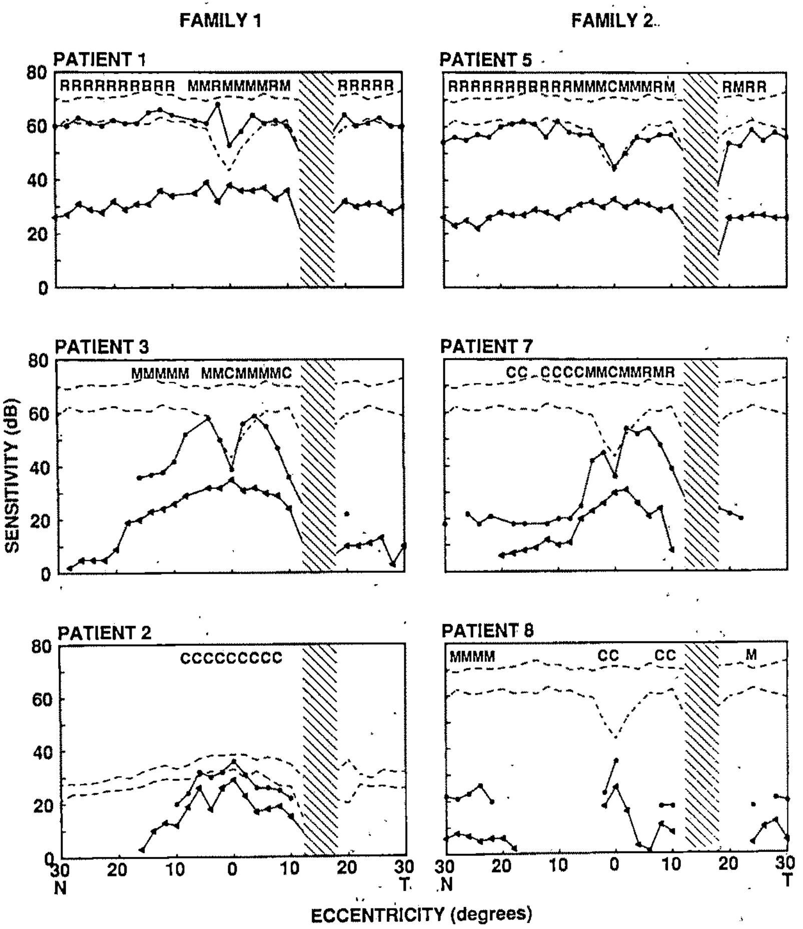

Fig. 3 (Kemp and associates). Two-color dark-adapted static perimetric profiles along the horizontal meridian for the central 60 degrees. Left, Patients 1, 3, and 2, representing three generations of Family 1. Right, Patients 5, 7, and 8, representing three generations of Family 2. Circles indicate 500 nm and triangles indicate 650 nm. For Patients 1, 3, 5, 7, and 8, dotted lines delimit 2 standard deviations above and below the mean normal (N = 10; ages, 14 to 56 years) for 500 nm. For Patient 2, dotted lines delimit 2 standard deviations above and below the mean normal for 650 nm at the cone plateau (N = 5; ages, 29 to 54 years). The photoreceptor mediations for detection of the stimuli are indicated by the row of letters on the graphs. R indicates rods detected both, M indicates mixed (that is, rods detected 500 nm and cones detected 650 nm), C indicates cones detected both. Hatched bars represent the physiologic blind spot. N indicates nasal and T indicates temporal.

tient 1 in degree of dysfunction, but rod sensitivities were below the normal limits at most loci. Her father, Patient 7, had a more advanced stage of dysfunction with only a few paracentral rod- and mixed-mediated loci, most of which had abnormally reduced sensitivity to 500 nm, and only cone-mediated loci or no measurable function at greater eccentricities. Patient 8, the grandfather of Patient 5, had a small central island of abnormal cone function and some mixed-mediated function (although reduced in sensitivity for the rods by approximately 4 log units) beyond a paracentral scotomatous region.

Dark adaptometry in all patients disclosed an abnormally long recovery period after extensive light adaptation (Fig. 4). Adaptometry was performed on one member each of Families 1 and 4, two members of Family 2, and three members of Family 3. For the light-adapting exposure used, normal subjects showed complete recovery of sensitivity after approximately 55 minutes in darkness (Fig. 4, dashed curves), a duration similar to previously published findings.[11,15,24] Dark-adaptation data from Patient 1, who had only minimal rod dysfunction throughout the retina, were compared to those from Patient 13, who had a severely constricted visual field with rod function measurable only in her small central island (Table). In each case, the kinetics of sensitivity recovery were similar, although in Patient 13 the reduction in rod sensitivity caused by the light exposure was slightly greater than that in Patient 1 during most of the recovery period. In both patients, recovery of rod sensitivity to within 2 dB of baseline dark-adapted levels was reached after between 160 and 210 minutes.

Intrafamilial consistency of this rod adaptation abnormality was apparent in two families (Fig. 4). The two members tested from Family 2 (Patients 4 and 5) showed recovery to within 2 dB of the baseline dark-adapted level in approximately 200 minutes. The three members tested from Family 3 showed similar results (Fig. 4). Recoveries of rod sensitivity in Patients 9 and 11 closely paralleled each other and those observed in Patients 1, 4, 5, and 13, with levels

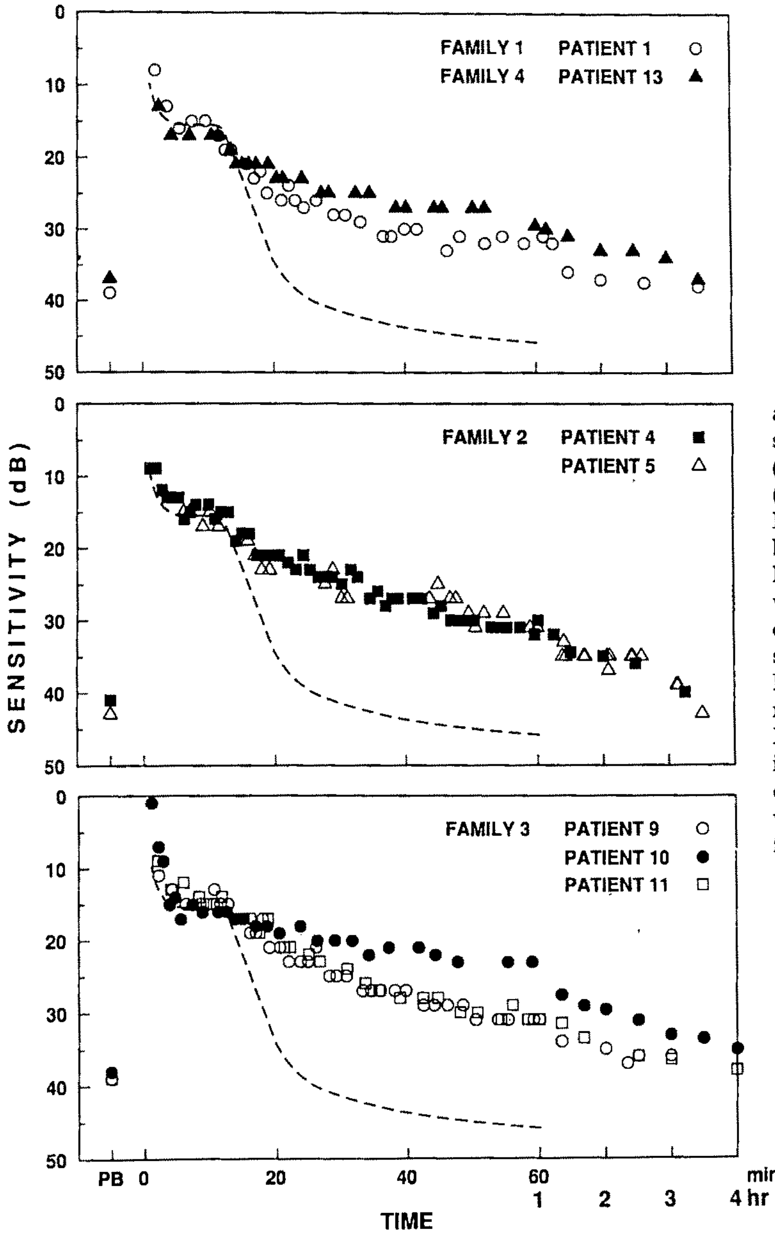

Fig. 4 (Kemp and associates). Dark adaptometry in Patients 1 and 13, representing Families 1 and 4, respectively (top); Patients 4 and 5 from Family 2 (center); and Patients 9 through 11 from Family 3 (bottom). PB indicates prebleach measurement obtained after at least three hours of dark adaptation and without previous light exposure. The dashed curves are the mean recovery of sensitivity of two normals, fitted by eye. Patient 13 was tested at 5 degrees in the nasal field with a 500-nm stimulus and Patient 10 was tested at 10 degrees in the inferior field with a 460-nm stimulus. All other patients and the normal subjects were tested at 12 degrees in the inferior field with a 460-nm stimulus.

within 2 dB of those before light exposure attained in 180 minutes. In the third member of Family 3 (Patient 10), rod sensitivity during dark adaptation showed relatively greater depression than was seen for the other six patients (Fig. 4) and recovery required approximately 300 minutes.

Imaging fundus reflectometry was performed in Patients 5, 7, and 11. In Patient 5, rod sensitivity was within 7 dB of normal at each of the test loci within the measurement area and corresponding levels of rhodopsin were between 30% and 60% of those obtained from the same retinal region of a normal subject (Fig. 5). Patient 11 had a wide range of rod dysfunction (5 dB to > 35 dB) within the area tested; pigment levels varied from approximately 22% of normal to barely detectable. In Patient 7, whose rod sensitivity loss was > 40 dB throughout the test area, rod pigment was not clearly present: data were below the reliable measurement limits. The solid line in Figure 5 is the curve that would be expected to define the relationship between reduced levels of rhodop-

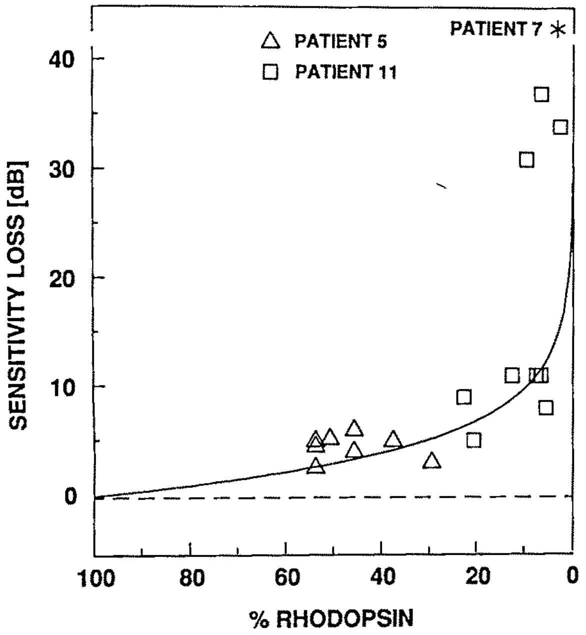

Fig. 5 (Kemp and associates). The relationship between the reduction of visual sensitivity and rhodopsin levels in Patients 5 (triangles) and 11 (squares). Data points represent values obtained from individual locations within the measurement area. Rod sensitivity loss was determined by subtracting patient data from mean results of normal subjects (N = 4; ages, 23 to 31 years) with the 500-nm stimulus. The asterisk indicates rhodopsin levels were unmeasurably low within the area examined by fundus reflectometry, and dark-adapted visual function was mediated by cones in Patient 7. The solid line represents the expected relationship if the reduction in visual sensitivity was caused solely by the decreased probability of light absorption resulting from reduced levels of rhodopsin.

sin and the loss of sensitivity resulting from the decreased absorption of incident light. The data from the patients lie relatively close to this line.

Discussion

Results of electroretinography and kinetic perimetry in our patients confirmed the variability in severity of expression that is known to occur in autosomal dominant phenotypes[28] and has been reported to occur within and between families carrying the P23H rhodopsin mutation.[9] As noted previously, the abnormalities in rod and cone electroretinogram amplitude and timing were not specific for this mutation or for this genetic type.[9,14,29] Kinetic perimetry results in our patients confirmed an altitudinal pattern of dysfunction in patients with the P23H rhodopsin mutation.[8] This pattern, however, was not a general finding for the mutation, nor was it specific to it; it was found in some members of Families 2 and 3 but not in others, and it has also been found in patients with other rhodopsin mutations.[11,14]

Dark- and light-adapted static perimetry and fundus reflectometry results provided insight into the nature and progress of the retinal degeneration in patients with the P23H rhodopsin mutation. In early stages of the disease, there was mildly abnormal rod sensitivity across the retina and cone sensitivity was within the normal range. Rhodopsin levels at this stage were decreased by amounts that indicated the reduced ability of the rods to absorb incident light accounted fully for the rods' diminished sensitivity. At intermediate stages, some retinal regions retained mild rod sensitivity loss and no cone sensitivity loss, whereas other regions progressed to more pronounced rod dysfunction and some cone dysfunction. Visual pigment measurements in regions that included both mild and more pronounced rod dysfunction showed changes in rhodopsin that paralleled the losses in sensitivity. The regional quality of the disease at this stage and the relationship of rhodopsin to visual sensitivity would likely have qualified patients with the P23H rhodopsin mutation to be classified as having type 2 or regionalized autosomal dominant retinitis pigmentosa, according to a scheme used to subclassify such patients before genotypes became known.[30,31] Advanced stages of the disease are characterized by severe visual loss and regions of residual function with little or no rod function, no measurable rhodopsin, and abnormal cone function.

Perhaps the most salient characteristic of the patients examined in our study was the abnormally long period required for their rods to adapt to the dark after intense light adaptation. The pattern of recovery of sensitivity in the patients was consistent between the four families. In each case, the transition from cone to rod mediation was identifiable by an increase in sensitivity of approximately 5 dB between the 15th and 20th minutes of dark adaptation (Fig. 4). After that time, rod sensitivity drifted back to the pre–light-adaptation levels over a period of approximately three hours in six of the patients. In Patient 10, although the recovery pattern was qualitatively similar to that of the other patients, the rod sensitivity depression was more pronounced throughout the rod branch of dark adaptation, and recovery took nearly two hours longer. We speculate that the exacerbation of the abnormality may reflect that dark adaptation was measured close to the edge of the patient's remaining area of functioning rods, so that the rods may have been affected by processes resulting from the disease progression and distinct from the primary lesion.

We have previously reported discernible differences in patterns of dysfunction in patients with autosomal dominant retinitis pigmentosa who have point mutations at other amino acid positions in the rhodopsin molecule.[11] In patients with two of the mutations we examined, T17M and T58R, dark adaptation was also abnormally prolonged. Although some similarities exist between the abnormalities of the patients with the P23H mutation and those of the patients with the T17M and T58R mutations, the three phenotypes appear to differ quantitatively, at least among the subjects examined so far. In the patients with the T58R mutation, the initial phase of the rod branch of the dark-adaptation curve after substantial pigment bleaching was extensive and rapid, with recovery to within approximately 10 dB of fully dark-adapted sensitivity being attained after less than 20 minutes in darkness.[11] The subsequent recovery was abnormally long and required approximately 150 minutes. In a patient with the T17M mutation, although rod function was detectable within 20 minutes after the bleach, recovery of rod sensitivity to prebleach levels took nearly 24 hours.[11] Quantitative analysis of the kinetics of rod dark adaptation in sufficient numbers of patients with each of the mutations may clarify whether there are characteristics specific to each of them.[32,33]

ACKNOWLEDGMENT

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References

1. McWilliam, P., Farrar, G. J., Kenna, P., Bradley, D. G., Humphries, M. M., Sharp, E. M., McConnell, D. J., Lawler, M., Sheils, D., Ryan, C., Stevens, K. J., Daiger, S. P., and Humphries, P.: Autosomal dominant retinitis pigmentosa (ADRP). Localization of an ADRP gene to the long arm of chromosome 3. Genomics 5:619, 1989.

2. Dryja, T. P., McGee, T., Reichel, E., Hahn, L. B., Cowley, G. S., Yandell, D. W., Sandberg, M. A., and Berson, E. L.: A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature 343:364, 1990.

3. Dryja, T. P., McGee, T., Hahn, L. B., Cowley, G. S., Olsson, J. E., Reichel, E., Sandberg, M. A., and Berson, E. L.: Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa. N. Engl. J. Med. 323:1302, 1990.

4. Inglehearn, C. F., Bashir, R., Lester, D. H., Jay, M., Bird, A. C., and Bhattacharya, S. S.: A 3-bp deletion in the rhodopsin gene in a family with autosomal dominant retinitis pigmentosa. Am. J. Hum. Genet. 48:26, 1991.

5. Sung, C.-H., Davenport, C. M., Hennessey, J. C., Maumenee, I. H., Jacobson, S. G., Heckenlively, J. R., Nowakowski, R., Fishman, G., Gouras, P., and Nathans, J.: Rhodopsin mutations in autosomal dominant retinitis pigmentosa. Proc. Natl. Acad. Sci. U.S.A. 88:6481, 1991.

6. Keen, T. J., Inglehearn, C. F., Lester, D. H., Bashir, R., Jay, M., Bird, A. C., Jay, B., and Bhattacharya, S. S.: Autosomal dominant retinitis pigmentosa. Four new mutations in rhodopsin, one of them in the retinal attachment site. Genomics 11:199, 1991.

7. Dryja, T. P., Hahn, L. B., McGee, T. L., Cowley, G. S., and Berson, E. L.: Mutation spectrum of the rhodopsin gene among patients with autosomal dominant retinitis pigmentosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 890.

8. Heckenlively, J., Rodriguez, J. A., and Daiger, S. P.: Autosomal dominant sectoral retinitis pigmentosa. Two families with transversion mutation in codon 23 of rhodopsin. Arch. Ophthalmol. 109:84, 1991.

9. Berson, E. L., Rosner, B., Sandberg, M. A., and Dryja, T. P.: Ocular findings in patients with autosomal dominant retinitis pigmentosa and a rhodopsin gene defect (Pro-23-His). Arch. Ophthalmol. 109:92, 1991.

10. Berson, E. L., Rosner, B., Sandberg, M. A., Weigel-Franco, C., and Dryja, T. P.: Ocular findings in patients with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine. Am. J. Ophthalmol. 111:614, 1991.

11. Jacobson, S. G., Kemp, C. M., Sung, C.-H., and Nathans, J.: Retinal function and rhodopsin levels in autosomal dominant retinitis pigmentosa with rhodopsin mutations. Am. J. Ophthalmol. 112:256, 1991.

12. Weleber, R. G., Murphey, W. H., Rodriguez, J. A., Lovrien, E. W., Litt, M., and Daiger, S. P.: Phenotypic expression of pro23his mutation of rhodopsin in a large family with autosomal dominant retinitis pigmentosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 913.

13. Fitzke, F. W., Owens, S., Moore, A. T., Jay, M.,

Inglehearn, C. F., Bhattacharya, S. S., and Bird, A. C.: Comparison of functional characteristics of autosomal dominant retinitis pigmentosa with different amino acid changes in the rhodopsin molecule. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1991, p. 912.

14. Fishman, G. F., Stone, E. M., Gilbert, L. D., Kenna, P., and Sheffield, V. C.: Ocular findings associated with a rhodopsin gene codon 58 transversion mutation in autosomal dominant retinitis pigmentosa. Arch. Ophthalmol. 109:1387, 1991.

15. Alexander, K. R., and Fishman, G. A.: Prolonged rod dark adaptation in retinitis pigmentosa. Br. J. Ophthalmol. 68:561, 1984.

16. Ernst, W., Kemp, C. M., and Moore, A. T.: Abnormal dark adaptation and rhodopsin regeneration in autosomal dominant retinitis pigmentosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1987, p. 236.

17. Moore, A. T., Fitzke, F. W., Chen, J. C., Kemp, C. M., and Bird, A. C.: Prolonged rod dark adaptation in autosomal dominant sector retinitis pigmentosa. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis Sci. Philadelphia, J. B. Lippincott, 1989, p. 45.

18. Jacobson, S. G., Yagasaki, K., Feuer, W. J., and Roman, A. J.: Interocular asymmetry of visual function in heterozygotes of X-linked retinitis pigmentosa. Exp. Eye Res. 48:679, 1989.

19. Jacobson, S. G., Borruat, F.-X., and Apâthy P. P.: Patterns of rod and cone dysfunction in Bardet-Biedl syndrome. Am. J. Ophthalmol. 109:676, 1990.

20. Yagasaki, K., and Jacobson, S. G.: Cone-rod dystrophy. Phenotypic diversity by retinal function testing. Arch. Ophthalmol. 107:701, 1989.

21. Jacobson, S. G., Voigt, W. J., Parel, J.-M., Apáthy, P. P., Nghiem-Phu, L., Myers, S. W., and Patella, V. M.: Automated light- and dark-adapted perimetry for evaluating retinitis pigmentosa. Ophthalmology 93:1604, 1986.

22. Apáthy, P. P., Jacobson, S. G., Nghiem-Phu, L., Knighton, R. W., and Parel, J.-M.: Computer-aided analysis in automated dark-adapted perimetry. In Greve, E. L., and Heijl, A. (eds.): Seventh International Visual Field Symposium. Dordrecht, The Netherlands, Martinus Nijhoff Publishers, 1987, pp. 279–284.

23. Massof, R. W., and Finkelstein, D.: Rod sensitivity relative to cone sensitivity in retinitis pigmentosa. Invest. Ophthalmol. Vis. Sci. 18:263, 1979.

24. Pugh, E. N.: Rhodopsin flash photolysis in man. J. Physiol. 248:393, 1975.

25. Faulkner, D. J., and Kemp, C. M.: Human rhodopsin measurement using a TV-based imaging fundus reflectometer. Vision Res. 24:221, 1984.

26. Kemp, C. M., Faulkner, D. J., and Jacobson, S. G.: Visual pigment levels in retinitis pigmentosa. Trans. Ophthalmol. Soc. U.K. 103:453, 1984.

27. Kemp, C. M., Jacobson, S. G., and Faulkner, D. J.: Two types of visual dysfunction in autosomal dominant retinitis pigmentosa. Invest. Ophthalmol. Vis. Sci. 29:1235, 1988.

28. Thompson, J. S., and Thompson, M. W.: Genetics in Medicine, ed. 4. Philadelphia, W. B. Saunders Company, 1986, p. 65.

29. Berson, E. L.: Retinitis pigmentosa and allied retinal diseases. Electrophysiological findings. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:659, 1976.

30. Massof, R. W., and Finkelstein, D.: Two forms of autosomal dominant primary retinitis pigmentosa. Doc. Ophthalmol. 51:289, 1981.

31. Lyness, A. L., Ernst, W., Quinlan, M. P., Clover, G. M., Arden, G. B., Carter, R. M., Bird, A. C., and Parker, J. A.: A clinical, psychophysical and electroretinographic survey of patients with autosomal dominant retinitis pigmentosa. Br. J. Ophthalmol. 69:326, 1985.

32. Lamb, T. D.: The involvement of rod photoreceptors in dark adaptation. Vision Res. 21:1773, 1981.

33. Stabell, U., Stabell, B., and Nordby, K.: Rod and cone dark adaptation. Clin. Vision Sci. 5:345, 1990.

Ultramicrosurgical Removal of Subretinal Hemorrhage in Cats

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Subretinal hemorrhages are associated with progressive degeneration of the outer retina and a corresponding poor visual prognosis. Mixed results have been reported in previous attempts to remove such subretinal hemorrhages. We developed an ultramicrosurgical system that used the control of a stereotactic micromanipulator to direct a micropipette tip through a small retinotomy into the subretinal space in three cat eyes. Low-dose recombinant tissue plasminogen activator was then introduced into the subretinal space around the subretinal hemorrhage via a controlled microinfusion system. The recombinant tissue plasminogen activator solution facilitated clot lysis and subsequent removal through the micropipette. Light- and electron-microscopic analysis of histopathologic specimens disclosed good preservation of retinal architecture in the three cat eyes in which experimental subretinal hemorrhages were removed. This was in contrast to the retinal degeneration observed in similar but untreated experimental subretinal hemorrhages.

MASSIVE SUBRETINAL HEMORRHAGES are associated with a poor visual prognosis[1] that is most likely caused by a degeneration of the outer retina.[2,3] Accordingly, various surgical approaches have been tried to extract these subretinal clots. These approaches have involved either the use of 20- to 30-gauge cannulas to wash out or evacuate the subretinal blood or forceps to grasp and remove the solid clot or semiliquid blood.[4-10] With any of these techniques, a retinotomy that is at least 310 μm in size is required (30-gauge cannula). A retinal hole of this size typically requires some form of retinopexy and tamponade with intraocular gas or silicone oil to ensure reattachment of the retina. A retinotomy of this size also increases the risk of retinal redetachment and proliferative vitreoretinopathy.[10,11]

We developed an ultramicrosurgical system that uses the control of a stereotactic micromanipulator to direct a micropipette with a 50- to 65-μm outer-diameter tip across the vitreous, through the retina, and into the subretinal space in cats. With this system it is possible to infuse or evacuate various fluids from the subretinal space in a controlled fashion. Using this approach, we infused recombinant tissue plasminogen activator beneath the retina to lyse and remove one- and two-day-old subretinal clots in cats.

Methods

We used 3- to 6-month-old, domestic shorthair cats according to the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Laboratory studies including a normal complete blood cell count with differential, platelet estimate, bleeding time, prothrombin time, and partial thromboplastin time were required for entry into the study. Fundus photography was performed pre- and postoperatively.

Creation of subretinal hemorrhages—A subret-

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inal hemorrhage was created in one eye of each cat by first making a subretinal bleb of balanced saline solution with a micropipette and then passing a 20-gauge needle through the posterior sclera and choroid and into the bleb and withdrawing the needle to allow choroidal bleeding into the subretinal space as previously described.[2] Routine veterinary and ophthalmic care was provided pre- and postoperatively as reported previously.[2]

Micropipette fabrication—The glass micropipettes were created from 1.5-mm, thin-walled capillary tubes that were cleaned with 1 M hydrochloric acid, rinsed with distilled water, and dried. The capillary tubes were then pulled into two micropipettes (micropipette puller, Kopf Instruments, Tujunga, California) and ground to the desired size on an air-driven grinding wheel[12] using wet 3-μm abrasive paper. The finished micropipettes were cleaned by suctioning acetone through them. The tips were inspected and measured with a standard light-microscope reticule, before placement in a micropipette storage tray for gas sterilization.

Ultramicrosurgical apparatus—The ultramicrosurgical system consisted of micropipettes connected to a syringe pump apparatus and positioned by a stereotactic micromanipulator. A glass micropipette with an outer diameter of 50 to 65 μm at the beveled tip was placed in an electrode coupler that was mounted in a modified Kreiger and Straatsma vitreoretinal stereotactic micromanipulator (Fig. 1).[13] The stereotactic manipulator provided precision adjustments along two arcs of movement on the side arms and the x, y, and z axes. Standard intravenous tubing was used to connect the electrode coupler to a syringe pump (Harvard Apparatus, South Natick, Massachusetts). The syringe pump was set at 5 μl/min for infusion and between 5 and 200 μl/min for aspiration. Intraoperatively, the cat's head was taped to a fitted foam rubber cushion to stabilize it during the procedure, which was conducted with the cat under general anesthesia achieved by intu-

Subretinal hemorrhage removal—Three subretinal hemorrhages were removed with this system with each cat under general anesthesia achieved with halothane. A pars plana infusion line with balanced saline solution was placed inferotemporally and a pars plana incision was made. A posterior vitrectomy was performed with an automated vitrectomy system over the area of subretinal hemorrhage. With the micromanipulator system, the micropipette was positioned within the vitreous cavity immediately over the superior margin of the subretinal hemorrhage. The micropipette was then advanced through the neurosensory retina and into the clot with the microadvancement drive. Recombinant tissue plasminogen activator solution was infused at a rate of 5 μl/min with the syringe pump to prevent occlusion of the tip and to help define the entry into the subretinal space. A solution of either 10-μg/ml recombinant tissue plasminogen activator (one cat) or 200-μg/ml recombinant tissue plasminogen activator (two cats) in balanced saline solution was pumped into the subretinal space around the hemorrhage for 60 seconds (Fig. 2). Thus, the total dose of recombinant tissue plasminogen activator injected into the subretinal space ranged from 0.5 to 5 μg. The micropipette was removed from the eye; no fluid egressed or backflowed out of the bleb back into the vitre-

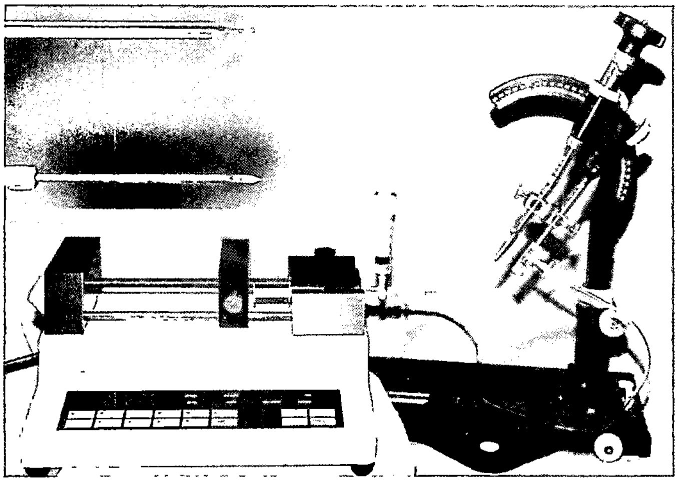

Fig. 1 (Toth and associates). The ultramicrosurgical apparatus. Basic elements include a syringe pump, intravenous connector tubing, an electrode coupler, and a glass micropipette. The electrode coupler and micropipette are held by a stereotactic manipulator. Inset, The difference in size between a glass micropipette with a 60-μm tip and the tip of a 20-gauge needle is shown.

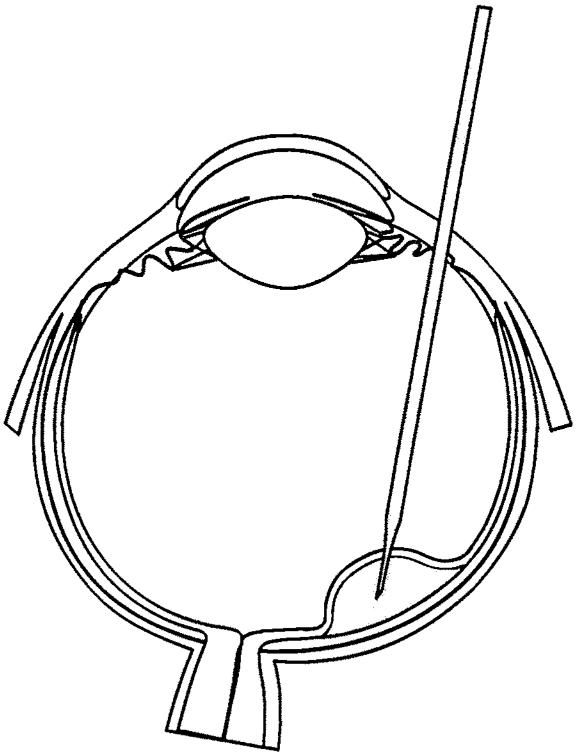

Fig. 2 (Toth and associates). Diagram of the approach to subretinal hemorrhage removal with a glass micropipette. The glass micropipette is inserted transvitreally through a sclerotomy and stereotactically manipulated through the subretinal space. Recombinant tissue plasminogen activator is injected through the micropipette and the subretinal hemorrhage is then aspirated through the micropipette after fibrinolysis has occurred.

ous. Within 20 minutes, the clot became gelatinous as it dissolved. A new micropipette with a 65- to 300-μm outer-diameter tip was similarly introduced into the subretinal space either through the previous pipette site or at a new margin of the lesion while infusing a balanced saline solution at a rate of 5 μl/min. The pump was switched to the aspirate mode and the admixture of blood, recombinant tissue plasminogen activator solution, and balanced saline solution was removed from the subretinal space. A thin film of blood often remained beneath the flattened retina. The micropipette system was removed from the eye, flushed free of blood, and reintroduced into the eye. To remove the remaining subretinal blood, the micropipette was advanced into the subretinal space while infusing balanced saline solution at a rate of 5 μl/min to stir up the remaining erythrocytes. This mixture was then evacuated from the subretinal space through the micropipette as before. This procedure was repeated up to three times during a given operation. Despite these efforts, shallow pockets of subretinal blood remained at the end of the operation. In one eye an air-fluid exchange was performed. The micropipette was removed from the eye and the sclerotomy and lateral canthotomy were closed. Standard ophthalmic and veterinary care was provided as previously described.[2] Postoperatively, the cats were monitored with ophthalmoscopy daily and fundus photography when possible for three days and then every two to three days. The cats were killed 14 days after subretinal hemorrhage removal with an intramuscular injection of ketamine hydrochloride, and an intravenous injection of pentobarbital. The eyes were immediately enucleated. The tissues were processed for light-microscopic analysis as previously described.[2]

Subretinal blood removal with metal needles—The previously described technique was also used with several types of metal cannulas instead of the glass micropipettes to attempt to remove subretinal hemorrhages in two eyes. Blunt cannulas and beveled sharp-tipped 25- to 33-gauge needles (210- to 520-μm outer diameter) were used. In all cases it was impossible to remove the subretinal blood through the metal needles, although we were able to inject the recombinant tissue plasminogen activator into the hemorrhages. The cats were killed and the eyes were enucleated.

Results

Clinical results—Before hemorrhage removal, the one- and two-day-old subretinal hemorrhages had the typically formed central coagulum with wrinkling of the overlying retina and an inferior collection of layered-out erythrocytes as reported in our subretinal hemorrhage study (Fig. 3).[2]

No apparent difference in the efficacy of fibrinolysis with either the 10 μg/ml or the 200 μg/ml of recombinant tissue plasminogen activator was observed. In all cases, the formed coagulum dispersed into a reddish mixture within five to 15 minutes after adding the recombinant tissue plasminogen activator solution. Leakage from the pipette entry site in the retina was not evident. No bleeding complications associated with the use of subretinal re-

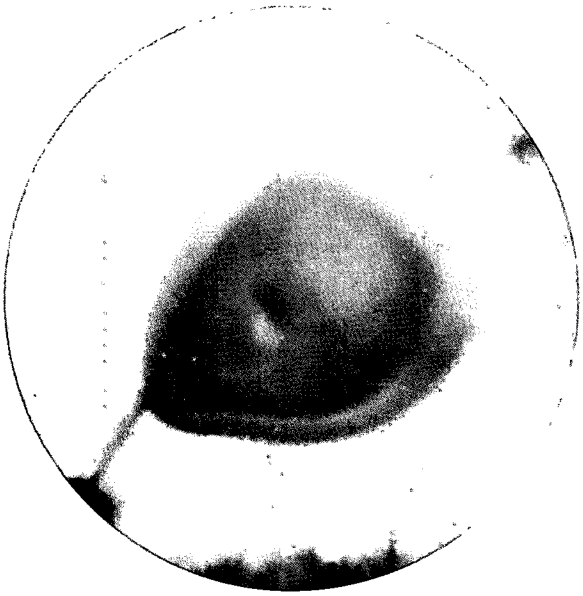

Fig. 3 (Toth and associates). Fundus photograph of a 30-minute-old experimental subretinal hemorrhage in a cat.

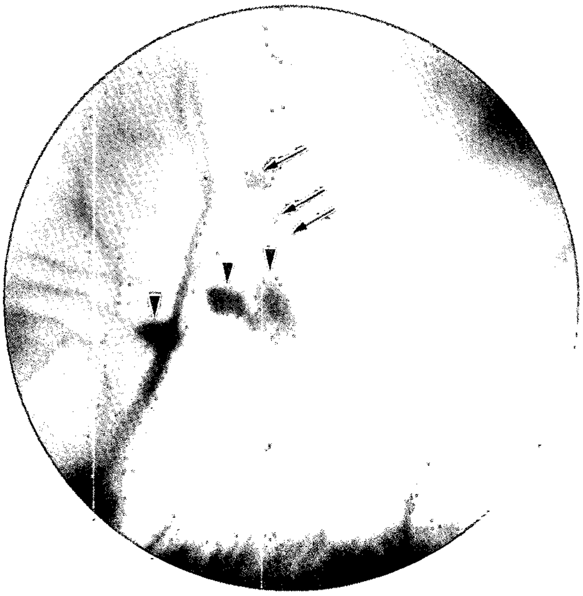

Fig. 4 (Toth and associates). Fundus photograph of the same eye shown in Figure 2, 14 days after removal of the experimental subretinal hemorrhage with recombinant tissue plasminogen activator. The black marks in the area of the previous subretinal hemorrhages are caused by changes in the tapetum from the transchoroidal puncture (arrows) and the micropipette contact (small arrows).

combinant tissue plasminogen activator were observed.

Using this ultramicrosurgical micropipette infusion and aspiration system, subretinal clots were successfully lysed and removed in three cat eyes. The lysed clot and saline mixture was readily aspirated through the micropipette system. Sometimes the blood–recombinant tissue plasminogen activator admixture occluded the glass micropipettes with tips with outer diameters of < 75 μm, but not with tips ≥ 75 μm in diameter. This may have been caused by microscopic bits of clot that occluded the micropipette tips, but were not grossly visible. Micropipette tips 60 to 100 μm in diameter readily passed through the retina into the clot, whereas larger tips (greater than 120 μm in diameter) tended to push the retina away from the pipette before passing through the retina. In preliminary in vitro and in vivo tests, the 30- to 33-gauge (inner diameter, 110 μm) 2-inch-long metal needles occluded with all attempts to withdraw lysed clots.

A small focus of subretinal blood remained after the initial withdrawal in all cases because of a loss of communication through the subretinal space as the retina flattened around the micropipette tip. Redetaching the retina over the entire lysed clot area using slow infusion of balanced saline solution through the micropipette system allowed further access to these areas and a more complete removal of the remaining hemorrhagic foci.

Clinically, the retina was completely reattached over the area of previous subretinal hemorrhage within 36 hours of treatment (Fig. 4). Dark tapetal marks were observed at the sites of previous choroidal perforations that had created the initial hemorrhage. Even finer tapetal marks were seen at the site of micropipette retinotomies. Twenty-four to 36 hours postoperatively, mild wrinkling of the retina was visible, which resolved over the next seven to 12 days. In the eye with a thin residual rim of blood, wrinkling cleared after an additional four days. By Day 8 to Day 12 it was difficult to discern the area involved with the previous subretinal hemorrhage from the adjacent normal retina except for the tapetal marks previously noted. During the two weeks after hemorrhage removal, no rebleeding or vitreous hemorrhage developed.

Histopathologic results—Tissue sections from the area involved with the original subretinal hemorrhage were examined with light and electron microscopy 14 days after subretinal hemorrhage removal. In all three eyes the retinal architecture was intact except for foci with

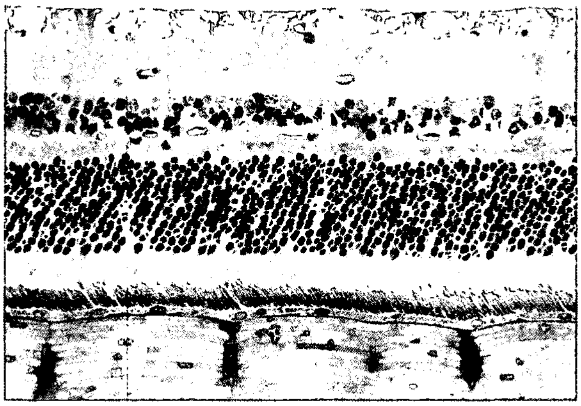

Fig. 5 (Toth and associates). A histologic section of a retina 14 days after removal of an experimental subretinal hemorrhage with recombinant tissue plasminogen activator. The photograph illustrates a full-thickness section of a retina taken from a region that was previously overlying an experimental subretinal hemorrhage that was removed after two days. The cellular architecture is intact except for enlargement of some of the retinal pigment epithelium and a decreased length of the photoreceptor outer segments.

minor changes involving the retinal pigment epithelium–photoreceptor complex (Fig. 5). In these foci the photoreceptor outer segments were short and irregularly aligned as compared to the unoperated-on control sections. Infrequently, a 20- to 40-µm focus of red blood cells or amorphous debris was observed within the subretinal space. With electron microscopy, the photoreceptor outer segments varied from a normal appearance in most areas, to a few sites where they were abnormally short, with some vacuolization and mild distortion (Fig. 6). These changes were accentuated over the foci of residual subretinal material. The retinal pigment epithelial cells were mildly distended, but appeared to be normal otherwise. The photoreceptor inner segments and the remaining inner retinal architecture were ultrastructurally intact.

Discussion

Evacuation of an experimental subretinal hemorrhage with minimal trauma to the retina was demonstrated using an ultramicrosurgical system to inject recombinant tissue plasminogen activator solution under the retina and to remove the lysed clot. Differences between this approach and those previously reported include the following: (1) injection of low-dose recombinant tissue plasminogen activator solution and evacuation of lysed clot through a micropipette with a small tip that produced a self-sealing approximately 200- to 300-µm retinal hole; (2) use of a micromanipulator to minimize retinal and retinal pigment epitheli-

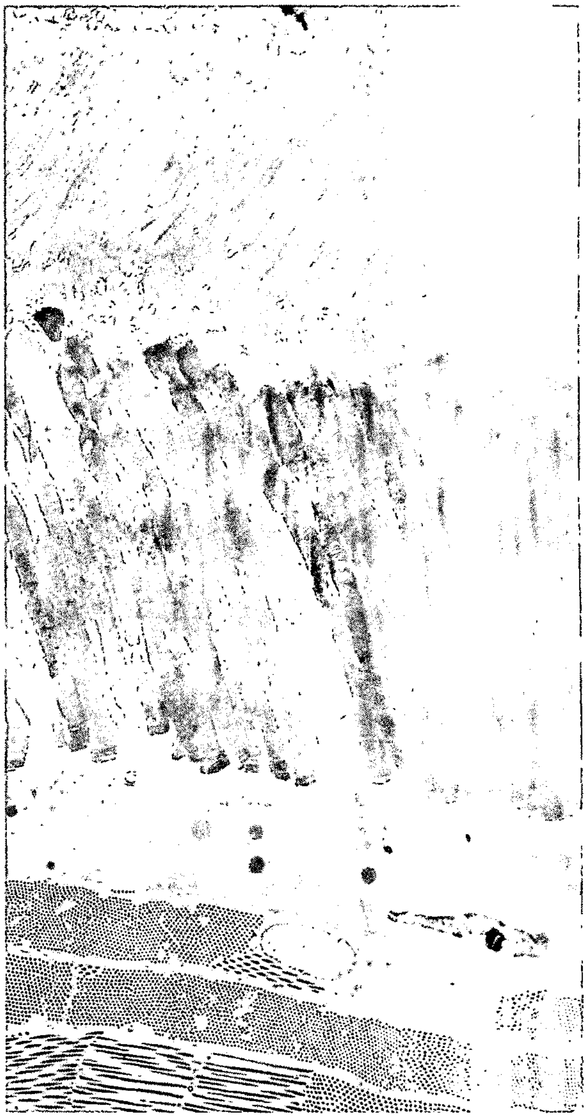

Fig. 6 (Toth and associates). Electron micrograph of a retina 14 days after removal of an experimental subretinal hemorrhage with recombinant tissue plasminogen activator. The photograph shows preservation of the retinal pigment epithelium, photoreceptor outer segments, and photoreceptor inner segments from a region that was previously detached over a two-day-old experimental subretinal hemorrhage (× 3,300).

um trauma while in the subretinal space; and (3) a controlled microinfusion system to minimize trauma from rapid irrigation.

We previously demonstrated that recombinant tissue plasminogen activator solution at a concentration of 1,000 μg/ml is toxic in the subretinal space of cats, whereas doses ≤ 200 μg/ml are nontoxic.[14] Intravitreally administered recombinant tissue plasminogen activator has been used in humans in doses up to 25 μg to lyse large fibrin clots[15,16] and in animal experimental models of subretinal treatment without hemorrhage removal.[17,18] Although recombinant tissue plasminogen activator solution was continuously pumped while we manipulated the micropipette within the vitreous cavity (never longer than 15 minutes with a maximal intravitreal dose of 15 μg), no abnormal intraoperative or postoperative bleeding was observed. Additionally, recombinant tissue plasminogen activator toxicity to the retina involved with the subretinal hemorrhage or to the uninvolved retina was not histopathologically evident.

Features of the glass micropipette that make it ideal for this procedure include the following: (1) its ability to be drawn into a small tip, (2) a low resistance to fluid flow, and (3) a transparent wall. The micropipette tip can be ground to any size ranging from 3 to 300 μm with a microgrinding system. The outer diameter of the micropipette tips that we created was about one-fifth the size of the smallest available metal cannula tip. This small micropipette tip slipped easily through the retina without any need for a preliminary retinotomy. Marmor and associates[19] have demonstrated that retinal holes from micropipettes 50 μm or smaller in diameter do not result in a discernible loss of subretinal solution. Work in our laboratory suggests that tips with an outer diameter as large as 200 μm will also produce self-sealing holes in the retinas of cats (unpublished data). The smaller retinal hole created by the guided micropipette prevented loss of the recombinant tissue plasminogen activator solution from the subretinal space, maximizing its duration of contact with the clot. Application of low-dose recombinant tissue plasminogen activator solution may not be as effective with other techniques that use a larger-bore cannula and larger retinotomy sites because greater amounts of the recombinant tissue plasminogen activator solution may be lost around the cannula at the retinotomy site.

The smallest metal needles that are currently available are 33 gauge with a 210-μm outer-diameter tip. The beveled metal tips of these needles are long and can easily enter the choroid before the inner lumen of the needle has completely penetrated the retina. A 33-gauge cannula with a blunt metal tip deflected the retina ahead of the needle into the choroid before penetrating the retina with excessive injury to both tissues. Once in the subretinal space, the 210-μm blunt tip was, however, effective for subretinal infusion.

Another benefit of the glass micropipette was that it seldom clogged while aspirating the subretinal blood (when > 75 μm in outer diameter). In part, this was caused by the contours of the micropipettes. Despite the small lumen at the tip, the resistance to fluid flow is low because of the short length of this narrowed lumen (< 1 mm) and the rapid increase in the inner diameter to a size of almost 1,400 μm just beyond it. In contrast, the metal needles occluded in all attempts to withdraw blood both in vitro and in vivo.

The transparent glass also allowed for excellent visualization while removing subretinal blood. The metal system provided no visualization to identify movement of blood or sites of occlusion in the lumen.

One drawback to the glass micropipette is the large (1.5-mm) outer diameter of the hub that requires a larger-than-standard sclerotomy. Another drawback is the potential for the glass micropipette to break inside of the eye. One micropipette broke at the point of attachment to the electrode holder and was removed from the eye without complication. The micropipette tip might also fracture while entering the sclerotomy site. The risk of broken glass within the eye is a concern in any potential operation. Accordingly, a micropipette cover might be beneficial in protecting the glass system during entry and removal from the eye.

We found the degree of precision and fine control offered by the micromanipulator to be improved over the standard surgical techniques. This equipment provided controlled advancement and retraction of the surgical tip by micrometers rather than millimeters, resulting in less trauma to the eye. Conversely, freehand surgical manipulation allows more rapid and flexible movement in approaching the retina, but may tear the retina and injure subretinal structures during lengthy subretinal procedures as a result of tremor.

The added benefit of the microinfusion and microwithdrawal pump in this system was the precise flow control it provided. This allowed a steadier rate of subretinal infusion and prevented an uncontrolled rapid detachment of the retina. This may be important in preventing the loss of retinal pigment epithelial cells by vigorous subretinal infusion. Vigorous subretinal infusion has been used experimentally to remove the retinal pigment epithelium from Bruch's membrane in preparation for retinal pigment epithelial transplantation.[20] It would seem prudent, therefore, to maintain a gentle flow of solutions beneath the retina to avoid such retinal pigment epithelial damage. This may be responsible, in part, for the relative histopathologic preservation of the three eyes of our cats at 14 days.

This ultramicrosurgical system removed subretinal hemorrhages with a minimum of retinal pathologic sequelae. The relatively intact retinal architecture of the three eyes in which the experimental subretinal hemorrhage was removed was in sharp contrast to the retinal degeneration observed over similar, but untreated experimental subretinal hemorrhages[2] and to the poor retinal preservation in other experimental subretinal hemorrhage treatment studies.[17,18] The areas of mild photoreceptor outer segment changes that we observed after hemorrhage removal were similar to those observed in other models of experimental retinal detachment.[21,22] These changes probably represented reattachment and regeneration changes that might be expected to normalize over a greater time. However, even if these photoreceptor outer segment abnormalities would not improve with time, the condition of the outer retina was substantially better than that of untreated 14-day-old subretinal hemorrhages. Identically produced subretinal hemorrhages resulted in severe outer retinal degeneration with loss of photoreceptor outer segments, photoreceptor inner segments, and part of the outer nuclear layer by Day 14.[2] Although the three eyes in this study fared better than those that were untreated in our previous work,[2] a larger study will be necessary for a true histopathologic picture. We are currently evacuating experimental subretinal hemorrhages at later time intervals to define the window of opportunity during which this surgical intervention might be useful.

Although experimental at this time, some features of this approach might eventually be applicable to subretinal operations. Studies of human subretinal membrane and hemorrhage removal have had mixed results.[4-10,23] Advancing beyond the currently available instrumentation to an ultramicroscopic subretinal surgical system may help to improve the visual outcome in these cases.

References

1. Bennett, S. R., Folk, J. C., Blodi, C. F., and Klugman, M.: Factors prognostic of visual outcome in patients with subretinal hemorrhage. Am. J. Ophthalmol. 109:33, 1990.

2. Toth, C. A., Morse, L. S., Hjelmeland, L. M., and Landers, M. B.: Fibrin directs early retinal damage after experimental subretinal hemorrhage. Arch. Ophthalmol. 109:723, 1991.

3. Glatt, H., and Machemer, R.: Experimental subretinal hemorrhage in rabbits. Am. J. Ophthalmol. 94:762, 1982.

4. Han, D. P., Mieler, W. F., Schwartz, D. M., and Abrams, G. W.: Management of traumatic hemorrhagic retinal detachment with pars plana vitrectomy. Arch. Ophthalmol. 108:1281, 1990.

5. Hanscom, T. A., and Diddie, K. R.: Early surgical drainage of macular subretinal hemorrhage. Arch. Ophthalmol. 105:1722, 1987.

6. deJuan, E., Jr., and Machemer, R.: Vitreous surgery for hemorrhagic and fibrous complications of age-related macular degeneration. Am. J. Ophthalmol. 105:25, 1988.

7. Rathschuler, F., Rossi, P., Lai, S., Colacino, R., Retrogalli, F., Ciurlo, G., and Zingirian, M.: Degenerescence maculaire senile. Traitement chirurgical et aspects histopathologiques. J. Fr. Ophtalmol. 12:697, 1989.

8. Thomas, M. A., and Halperin, L. S.: Subretinal endolaser treatment of a choroidal bleeding site. Am. J. Ophthalmol. 109:742, 1990.

9. Wade, E. C., Flynn, H. W., Jr., Olsen, K. R., Blumenkranz, M. S., and Nicholson, D. H.: Subretinal hemorrhage management by pars plana vitrectomy and internal drainage. Arch. Ophthalmol. 108:973, 1990.

10. Vander, J. F., Federman, J. L., Greven, C., Slusher, M. M., and Gabel, V. P.: Surgical removal of massive subretinal hemorrhage associated with age-related macular degeneration. Ophthalmology 98:23, 1991.

11. McDonald, H. R., Lewis, H., Aaberg, T. M., and Abrams, G. W.: Complications of endodrainage retinotomies created during vitreous surgery for complicated retinal detachment. Ophthalmology 96:358, 1989.

12. Curry, F. E., Huxley, V. H., and Sarelius, I. H.: Techniques in the microcirculation. Measurement of permeability, pressure and flow. In Linden, R. J. (ed.): Cardiovascular Physiology. Ireland Ltd., Elsevier Scientific Publishers, 1983, pp. 1–34.

13. Kreiger, A. E., and Straatsma, B. R.: An ocular fixation device for freehand pars plana vitrectomy. Mod. Probl. Ophthalmol. 18:195, 1977.

14. Benner, J. D., Morse, L. S., Toth, C. A., Landers, M. B., Hjelmeland, L. M., and Landers, M. B.: Evaluation of a commercial rt-PA preparation in the subretinal space of the cat. Arch. Ophthalmol. 1991, in press.

15. Dabbs, C. K., Aaberg, T. M., Aguilar, H. E., Sternberg, P., Jr., Meredith, T. A., and Ward, A. R.: Complications of tissue plasminogen activator therapy after vitrectomy for diabetes. Am. J. Ophthalmol. 110:354, 1990.

16. Jaffe, G. J., Abrams, G. W., Williams, G. A., and Han, D. P.: Tissue plasminogen activator for postvitrectomy fibrin formation. Ophthalmology 97:184, 1990.

17. Lewis, H., Resnick, S. C., Flannery, J. G., and Straatsma, B. R.: Tissue plasminogen activator treatment of experimental subretinal hemorrhage. Am. J. Ophthalmol. 111:197, 1991.

18. Johnson, M. W., Olsen, K. L., and Hernandez, E.: Tissue plasminogen activator treatment of experimental subretinal hemorrhage. Retina 11:250, 1991.

19. Marmor, M. F., Porteus, M., Negi, A., and Immel, J.: Validation of a model of non-rhegmatogenous retinal detachment. Curr. Eye Res. 3:515, 1984.

20. Lopez, R., Gouras, P., Brittis, M., and Kjeldbye, H.: Transplantation of cultured rabbit retinal epithelium to rabbit retina used closed eye technique. Invest. Ophthalmol. Vis. Sci. 28:1131, 1987.

21. Anderson, D. H., Stern, W. H., Fisher, S. K., Erickson, P. A., and Borgula, G. A.: Retinal detachment in the cat. The pigment epithelial-photoreceptor interface. Invest. Ophthalmol. Vis. Sci. 24:906, 1983.

22. Anderson, D. H., Guerin, C. J., Erickson, P. A., Stern, W. H., and Fisher, S. K.: Morphological recovery in the reattached retina. Invest. Ophthalmol. Vis. Sci. 2:168, 1986.

23. Thomas, M. A., and Kaplan, H. J.: Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome. Am. J. Ophthalmol. 111:1, 1991.

OPHTHALMIC MINIATURE

Knowing he was coming, Peggy had decided against sunglasses, a sign of trust to leave them off. Her wall-eyes are naked to him, her face has this helpless look, turned full toward him while both eyes seem fascinated by something in the corners of the ceiling. He knows only one eye is bad but he never can bring himself to figure out which. And all around her eyes this net of white wrinkles the sunglasses usually conceal.

John Updike, *Rabbit Redux*
New York, Fawcett Crest Books, 1971, p. 99

Cellular Infiltration of the Vitreous in a Patient With X-linked Immunodeficiency With Increased IgM

Karla J. Johns, M.D., Donna S. Hummell, M.D., Thomas L. McCurley, M.D.,
and Alexander R. Lawton III, M.D.

We studied visual impairment caused by benign lymphoid infiltration of the vitreous bilaterally, as a complication of a primary immunodeficiency, X-linked immunodeficiency with increased IgM in an 8-year-old boy. Immunophenotyping of a vitreous aspirate showed a mixed cell population, including lymphocytes (T helper, suppressor-cytotoxic T cells, and B cells) and macrophages. Cultures of the vitreous were negative for bacterial or fungal pathogens. The vitreous infiltrates have been resistant to treatment with corticosteroids and cytotoxic agents.

X-LINKED IMMUNODEFICIENCY with increased IgM is an uncommon X-linked primary immunodeficiency characterized by markedly decreased or absent serum levels of IgG, IgA, and IgE, but normal or increased serum levels of IgM.[1-3] Affected patients have recurrent bacterial infections and hyperplasia of lymphoid tissue in the lungs and gastrointestinal tract. We studied visual impairment in a patient with this disorder caused by a predominantly lymphoid infiltration of the vitreous bilaterally.

Case Report

An 8-year-old boy had a three-week history of bilateral painless vision loss at initial examination. No previous history of eye disease or trauma existed. His medical history was notable for X-linked immunodeficiency with increased IgM and systemic lymphoid hyperplasia involving the gastrointestinal tract and lung. He had a history of recurrent systemic bacterial infections since the age of 6 months, including meningitis, septicemia, pneumonia, otitis, and sinusitis.

Lymphoid hyperplasia was a prominent part of his disease. He underwent multiple episodes of peripheral lymphadenopathy. In 1984, progressive hilar adenopathy and pulmonary infiltrates led to an open-lung biopsy, which showed lymphoid interstitial pneumonitis and follicular hyperplasia of hilar lymph nodes (Figs. 1 and 2). Nodular lymphoid hyperplasia of the small and large intestine was demonstrated by colonoscopy and was associated with chronic diarrhea (often bloody) and a protein-losing enteropathy. As a consequence of gastrointestinal loss and malabsorption, replacement therapy with intravenously administered IgG was ineffective. He was treated with intravenously administered IgG, 800 mg/kg of body weight semimonthly (four times the standard dosage), which resulted in a serum IgG concentration of less than 250 mg/dl.

In addition to intravenously administered IgG, his regular treatments included oral administration of metronidazole to control intestinal bacterial overgrowth, oral administration of trimethoprim-sulfa or ampicillin for suppression of chronic bronchitis, and oral administration of moderate doses of prednisone given on alternate days in an attempt to control lymphoid hyperplasia and the related protein-losing enteropathy. A trial of treatment with low-dose orally administered methotrexate was attempted but discontinued when he developed mild thrombocytopenia and had shown no resolution of diarrhea.

On examination the child had a cushingoid

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From the Departments of Ophthalmology (Dr. Johns), Pediatric Immunology (Drs. Hummell and Lawton), and Pathology (Dr. McCurley), Vanderbilt University Medical Center, Nashville, Tennessee. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York (Dr. Johns).

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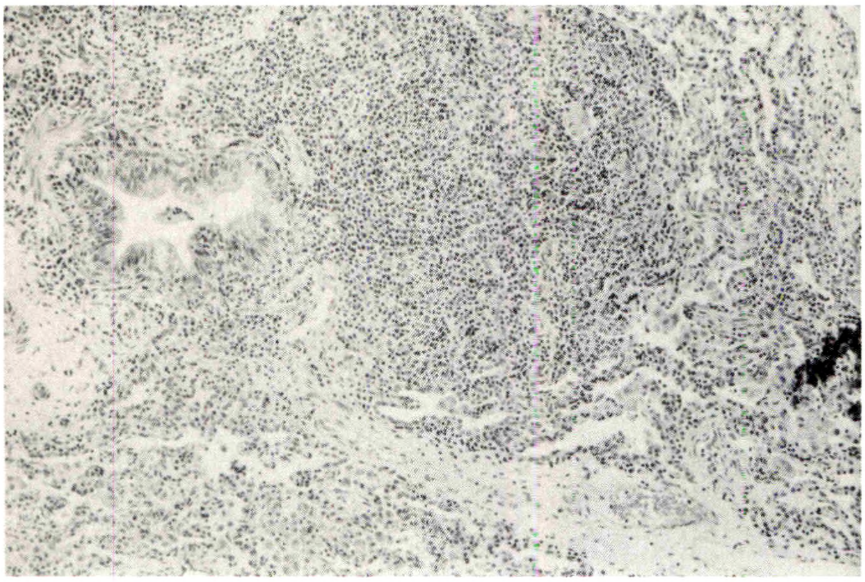

Fig. 1 (Johns and associates). Histologic section of biopsied lung tissue shows peribronchial lymphoid infiltrate (hematoxylin and eosin, × 100).

habitus. Visual acuity was 20/200 bilaterally. Pupillary light reflexes were normal. Results of anterior segment examination were normal; specifically, no cells or flare were observed in the anterior chamber of either eye. Ocular alignment and motility were normal. Marked bilateral cellular infiltration of the vitreous was observed, obscuring visualization of the posterior pole (Fig. 3). The density of the cellular infiltrate reduced visualization of the posterior pole to 20/200 with direct ophthalmoscopy. The retina and optic nerve appeared normal bilaterally, and the retinal vessels appeared moderately tortuous. Serologic testing was nondiagnostic because of the patient's disease and treatment regimen of semimonthly pooled immunoglobulin infusion. A computed tomographic scan of the head and orbits was normal, as was an ultrasonographic B-scan of both eyes. Results of visual-evoked response testing, using both flash and pattern full-field stimulation, were normal in both eyes.

A diagnostic aspirate of the vitreous of the left eye was obtained. Cytologic examination of the aspirate disclosed small lymphocytes, macrophages, and degenerating parenchymal cells. Immunologic-typing studies were performed on cytospin preparations using an avidin-biotin

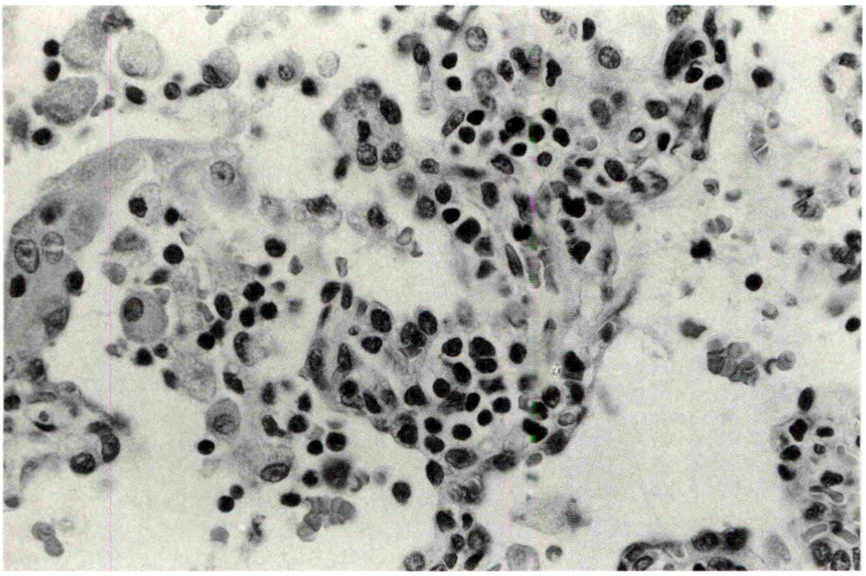

Fig. 2 (Johns and associates). Histologic section of biopsied lung tissue at higher power demonstrates extension of plasma cells and lymphocytes into alveolar walls (hematoxylin and eosin, × 600).

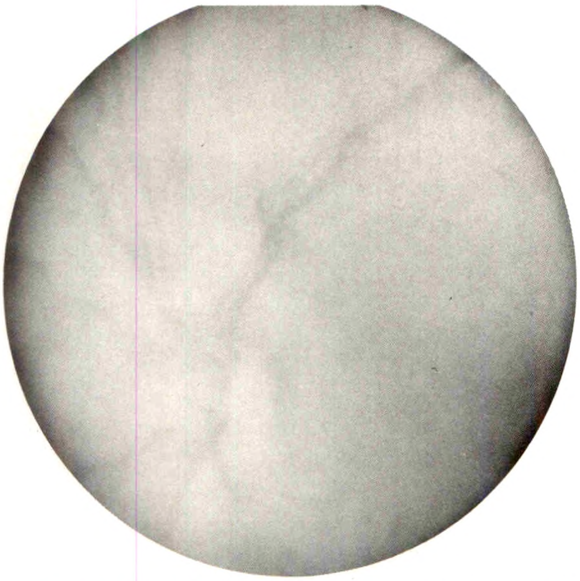

Fig. 3 (Johns and associates). Fundus photograph of the left eye demonstrating vitreous infiltrates markedly obscuring the visualization of the posterior pole. The appearance of both eyes is similar.

alkaline phosphatase method (Dako Corporation, Carpenteria, California) with primary monoclonal antibodies CD3, CD4, CD8, CD20, and CD14 (Becton-Dickinson, Franklin Lakes, New Jersey). Most lymphocytes were marked as T cells (CD3-positive) with a mix of T helper (CD4-positive) and T cytotoxic-suppressor cells (CD8-positive). Macrophages were CD14-positive with B cells (CD20-positive) identified infrequently (Fig. 4). The cytologic- and immunologic-typing studies were consistent with a reactive process. All cultures of the vitreous specimen for bacteria and fungi demonstrated no growth.

A trial of 40 mg of orally administered prednisone daily did not alter the vitreous infiltrate. Periocular injections of corticosteroid and corticosteroid eyedrops also failed to reduce the vitreous infiltrate. A brief trial of semimonthly intravenously administered infusions of cyclophosphamide also failed to lessen the vitreous infiltrate and had to be discontinued when the patient developed mild neutropenia.

Over the ensuing six months, the patient's visual acuity deteriorated but stabilized at 10/200 bilaterally, with a trace left relative afferent pupillary defect, decreased color perception, and mild optic disk pallor bilaterally. A subtotal vitrectomy was being considered as a treatment option, with this consideration balanced

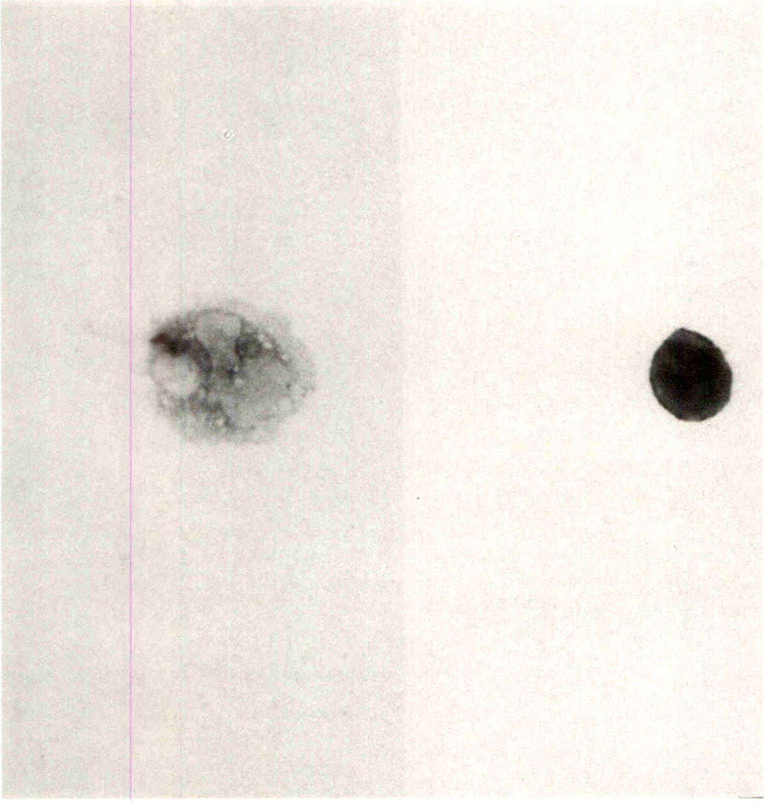

Fig. 4 (Johns and associates). Cytologic examination of a diagnostic aspirate of the vitreous of the left eye using monoclonal antibodies. Left, A monocyte (CD14-positive, × 1,000). Right, A T lymphocyte (CD3-positive, × 1,000; immunoalkaline phosphatase-alkaline phosphatase reaction with fuchsin red counterstain).

by concerns about anesthetic risk in this chronically ill child.

Discussion

Patients with X-linked immunodeficiency with increased IgM have normal numbers of circulating B cells bearing membrane-associated IgM and IgD, but lack B cells bearing membrane-associated IgG or IgA. Their B cells may be stimulated in vitro by polyclonal activators to proliferate and differentiate into IgM-secreting cells, but do not produce IgG or IgA. Although IgM antibodies are produced in vivo, pathogens are not effectively eliminated.[1] Persistence of foreign antigens provides the stimulus for continued proliferation of T and B cells, inducing the lymphoid hyperplasia so characteristic of this disease. In most patients, replacement therapy with intravenously administered IgG is succeeded by reduction in serum IgM and resolution of lymphoid hyperplasia. In our patient, severe protein-losing enteropathy has prevented adequate IgG replacement. We believe that bilateral vitreous infiltrates represent an unfortunate consequence of the pathophysiologic mechanisms inducing unregulated reactive lymphoid proliferation in this disease.

It is interesting to compare this syndrome to X-linked agammaglobulinemia (Bruton's disease). Boys with X-linked agammaglobulinemia have a defect that develops at an earlier stage of differentiation of B cells, and have few mature B lymphocytes in blood or lymphoid tissues.[1-3] Tonsils and lymph nodes are small and lack germinal centers. Although these patients have a similar spectrum of recurrent systemic bacterial infections, complications related to unregulated lymphoid hyperplasia do not develop.

Although bacterial conjunctivitis, retinal telangiectasia, and iritis have been previously reported in patients with X-linked agammaglobulinemia,[4,5] ocular abnormalities have not been well studied in patients with X-linked immunodeficiency with increased IgM. In this patient, unexplained infiltration of the vitreous bilaterally by lymphocytes and macrophages led to marked visual loss. Because no infectious agent responsible for the bilateral vitreal infiltration was recovered, we hypothesized that this patient's ocular disorder represents benign lymphoid hyperplasia in an unusual site.

References

1. Ochs, H. D., and Wedgewood, R. J.: Disorders of the B-cell system. In Stiehm, E. R., and Fulginiti, V. A. (eds.): Immunologic Disorders in Infants and Children. Philadelphia, W. B. Saunders Co., 1980, pp. 239–259.

2. Buckley, R. H.: Immunodeficiency diseases. JAMA 256:2841, 1987.

3. Rosen, F. S., Cooper, M. D., and Wedgewood, J. P.: The primary immunodeficiencies. N. Engl. J. Med. 311:235, 1984.

4. Hansel, T. T., O'Neill, D. P., Yee, M. L., Gibson, J. M., and Thompson, R. A.: Infective conjunctivitis and corneal scarring in three brothers with sex linked hypogammaglobulinaemia (Bruton's disease). Br. J. Ophthalmol. 74:118, 1990.

5. Frenkel, M., and Russe, H. P.: Retinal telangiectasia associated with hypogammaglobulinemia. Am. J. Ophthalmol. 63:215, 1967.

OPHTHALMIC MINIATURE

Heredity is obviously much on my mind these days, and should be. So I have been reading up on it some in a book that also deals with embryology. And I tell you: People who are wary of what they might find in a book if they opened 1 are right to be. I have just had my mind blown by an essay on the embryology of the human eye.

No combination of Time and Luck could have produced a camera that excellent, not even if the quantity of time had been 1,000,000,000,000 years! How is that for an unsolved mystery.

Kurt Vonnegut, *Hocus Pocus*
New York, Berkley Books, 1990, p. 82

Results

Pupillometric tracing was obtained in one subject (Fig. 1). Forceful eyelid closure for about five seconds caused a pupillary constriction that lasted more than six seconds. Pupillary redilatation began about 0.5 second after eyelid opening and consisted of an initial rapid phase lasting about 1.5 seconds succeeded by a slower phase.

Average pupillary constriction during forceful eyelid closure in each of the 30 normal subjects varied from −0.2 to 1.9 mm; the mean was 0.59 mm and the standard deviation was 0.55 mm (Fig. 2). Negative values indicated pupillary dilatation during eyelid closure. The two subjects with negative values were also the only subjects who showed a slight light reaction after eyelid opening; thus their pupillary dilatation during eyelid closure was most likely a response to darkness.

Pupillary constriction was considered clinically detectable in only nine of 30 subjects (30%), equivocal in four, and not detectable in 17. No correlation was found between the amplitude of pupillary constriction and average pupil size in darkness (Fig. 2) or age of subject.

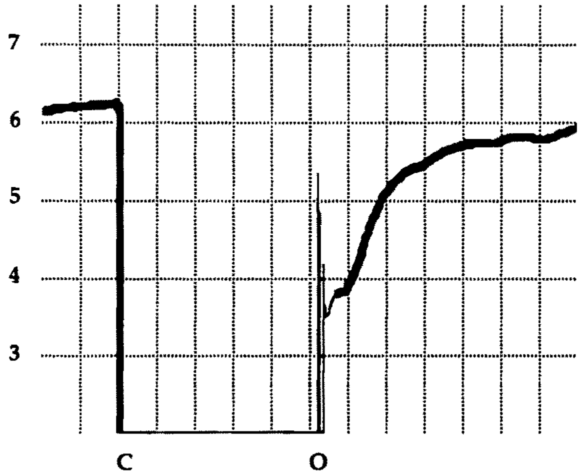

Fig. 1 (Cox and Digre). Pupillographic tracing of pupillary constriction during forceful eyelid closure in one normal subject. The numbers to the left indicate pupillary diameter in millimeters. Each vertical line represents one second. The eyelids closed at C and reopened at O, slightly more than five seconds later. Eyelid reopening created transient interference; valid recording is represented by the bold line in the trace.

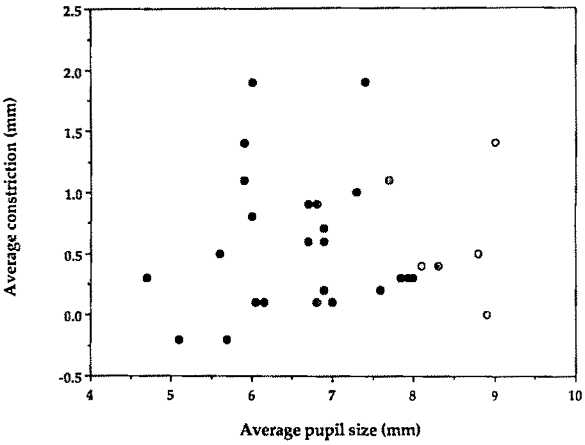

Fig. 2 (Cox and Digre). Pupillary constriction during forceful eyelid closure compared with pupil size. Each point represents the average of four measurements for a subject. Pupil sizes were measured in darkness.

Pupillary constriction to near was considered normal in 24 subjects and slight in six. One of these six subjects had a large (1.1 mm) pupillary constriction during eyelid closure; the other five had clinically undetectable constrictions.

Discussion

Observing pupillary constriction during forceful eyelid closure in a clinical setting is difficult. Piltz[5] used two different techniques in 23 normal subjects. First he looked at the pupils immediately after eyelid closure and saw constriction in only one case; then he held the eyelids open and saw constriction in eight cases (34.8%). However, with the first method the pupils constrict to light when the eyelids open after being closed, and this constriction may interfere with observation of constriction induced solely by forceful eyelid closure. With the second technique, it is not only difficult to decide whether the pupils are smaller, but also to view them. Because of these two problems, the clinician is most likely to see a convincing pupillary constriction in eyes with pupils that do not react to light; for example, when the eye is blind or there is pupillary light-near dissociation. In these cases, looking at pupillary diameter before and immediately after eyelid closure may detect the constriction.

Lowenstein and Loewenfeld[4] performed an experiment that they believed proved that the pupillary constriction induced by forceful eyelid closure was simply a near response. A subject who had this reflex was asked to fixate a target in the distance while forcefully closing his eyes. Under these conditions, no pupillary constriction was observed. Gifford[6] argued against the idea that this pupillary constriction is part of a near reflex. He pointed out that the eyes are usually divergent, not convergent, during forceful eyelid closure. We consider Lowenstein and Loewenfeld's results to be inconclusive; the failure of pupillary constriction while attempting to look at a target may have been caused by a reduced effort at eyelid closure.

Our interest in pupillary constriction during forceful eyelid closure was initiated by a young woman who had a tonic pupil that showed no response to light but showed strong constrictions during near effort and after forceful eyelid closure. Holmes[7] had described this combination of findings in five other subjects. These cases support the idea that the pathway from the brain to the eye for pupillary constriction during forceful eyelid closure is the same as that for accommodation, but whether this constriction is accompanied by other elements of the near triad has not been determined.

Looking for pupillary constriction after forceful eyelid closure may sometimes be helpful in assessing patients with abnormal pupils, particularly when the effort made by the patient to look at near objects seems weak. Conversely, the results of our study suggested that forceful eyelid closure is not a completely reliable method for eliciting pupillary constriction.

References

1. Lowenstein, O., and Givner, I.: Pupillary reflex to darkness. Arch. Ophthalmol. 30:603, 1943.

2. Duke-Elder, S., and Scott, G. I.: Neuro-Ophthalmology. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 12. London, Henry Kimpton, 1971, pp. 674–676.

3. von Graefe, A.: Notiz über die Behandlung der Mydriasis. Arch. Ophthalmol. 1:315, 1854.

4. Lowenstein, O., and Loewenfeld, I. E.: The pupil. In Davson, H. (ed.): The Eye, vol. 3. New York, Academic Press, 1969, pp. 255–337.

5. Piltz, J.: Ueber neue Pupillenphänomene. Neurol. Centralbl. 18:248, 1899.

6. Gifford, H.: An orbicularis pupillary reaction. Arch. Ophthalmol. 24:402, 1895.

7. Holmes, G.: Partial iridoplegia associated with symptoms of other disease of the nervous system. Trans. Ophthalmol. Soc. U.K. 51:209, 1931.

Immunofluorescent Staining and Corneal Sensitivity in Patients Suspected of Having Herpes Simplex Keratitis

Tatsuo Kodama, M.D., Seiji Hayasaka, M.D., and Tomoichi Setogawa, M.D.

We examined immunofluorescent staining and corneal sensitivity in 25 control subjects (25 eyes) with normal corneas, six patients (eight eyes) with possible herpes simplex keratitis, and 44 patients (48 eyes) with corneal lesions (recurrent erosion, superficial punctate keratitis, marginal ulcer, and follicular keratoconjunctivitis) in whom herpes simplex keratitis was not suspected. On immunofluorescent staining, all 25 control subjects had negative reactions, all eight eyes suspected of having herpes simplex keratitis had positive reactions, and 11 (23%) of the 48 eyes not suspected of having herpes simplex keratitis had positive reactions; the remaining 37 eyes had negative reactions. Of the 11 eyes not suspected of having herpes simplex keratitis but that had positive reactions on immunofluorescent staining, nine had recurrent erosions and the remaining two eyes had superficial punctate keratitis. Of the eight eyes with possible herpes simplex keratitis, seven (88%) had decreased corneal sensitivity. Of the 11 eyes not suspected of having herpes simplex keratitis but that had positive reactions on immunofluorescent staining, eight (73%) had decreased corneal sensitivity. Of the 37 eyes not suspected of having herpes simplex keratitis that had negative reactions on immunofluorescent staining, 11 (30%) had decreased corneal sensitivity.

THE DIAGNOSIS of herpes simplex keratitis is not always definite. Typical clinical findings, such as dendritic keratitis and decreased corneal sensitivity, are useful in making the diagnosis[1]; however, lesions without these findings cannot be excluded from the diagnosis. Immunostaining techniques recently have become available for use in the diagnosis of active herpes simplex keratitis.[2,3] We, therefore, examined immunofluorescent staining of herpes simplex virus antigen and corneal sensitivity in patients with corneal epithelial lesions.

Patients and Methods

We examined 50 patients with corneal epithelial lesions who initially were seen at our institution from January 1989 to December 1990. The corneal lesions were stained with fluorescein and were clinically evaluated by two of us (T.K. and S.H.). Lesions were then divided into the following two categories: (1) those suspected of being herpes simplex keratitis, including dendritic and geographic keratitis; and (2) those not suspected of being herpes simplex keratitis, including recurrent erosion, superficial punctate keratitis, marginal ulcer, and follicular keratoconjunctivitis. These lesions did not have dendritic edges or branching linear patterns. Twenty-five individuals with normal corneas served as the control subjects. Excluded from this study were patients in whom herpes simplex keratitis had been previously diagnosed by other ophthalmologists, those who had undergone ocular trauma or previous ocular operations, and those who wore contact lenses.

Immunofluorescent staining procedure—Eyedrops of 0.4% oxybuprocaine were instilled. A small piece of the corneal lesion was scraped with a 26-gauge needle, and spread evenly on glass slides. Two smears were obtained from each patient; one served as a control for staining. The material was air-dried, fixed in acetone for ten minutes, and air-dried again at room temperature (20 C). Immediately after being washed with phosphate-buffered saline solution (pH 7.3), the slides were incubated for one

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hour with normal swine serum (to prevent nonspecific staining with fluorescein-labeled swine antirabbit immunoglobulins), which was diluted 1:5 in phosphate-buffered saline solution. The serum was then tapped off, and the excess was wiped away. One slide was incubated with rabbit anti-herpes simplex virus type-1 antibodies (Dako, Denmark), diluted 1:20 in phosphate-buffered saline solution, and the other was incubated with normal rabbit serum overnight at 4 C as a control for staining. After three washings with phosphate-buffered saline solution, the smears were incubated with fluorescein-labeled swine anti-rabbit immunoglobulins (Dako, Denmark), and were diluted 1:20 in phosphate-buffered saline solution, for one hour at room temperature (20 C). After undergoing another wash, as described previously, coverslips were mounted with glycerol–phosphate-buffered saline solution, and the slides were examined with a fluorescence microscope.

Measurement of corneal sensitivity—Sensitivity of the affected lesion of the cornea was measured with a Cochet and Bonnet device without instillation of anesthetics, as described by Norn.[1]

Statistical analysis—The Student's *t*-test was used for statistical evaluation. Results were assumed to be significant if $P < .05$.

Results

The gender and age distribution were determined in 25 control subjects with normal corneas, in six patients suspected of having herpes simplex keratitis (five patients with dendritic keratitis and one with geographic keratitis), and in 44 patients without suspected herpes simplex keratitis (18 patients with recurrent erosion, 16 with superficial punctate keratitis, seven with marginal ulcer, and three with follicular keratoconjunctivitis). Twelve of the 25 control subjects were male and 13 were female. Three of the six patients suspected of having herpes simplex keratitis were male and three were female. Twenty-one of the 44 patients not suspected of having herpes simplex keratitis were male and 23 were female. The mean ages of the three groups were the following: control subjects, 65.7 years (range, 37 to 88 years); patients suspected of having herpes simplex keratitis, 64.5 years (range, 42 to 78 years); and patients not suspected of having herpes simplex keratitis, 57.1 years (range, 17 to 88 years). None of the control subjects' eyes were affected, eight of the eight eyes suspected of having herpes simplex keratitis were affected, and 48 of the 48 eyes not suspected of having herpes simplex keratitis were affected. No major difference was noted among the three groups.

Results of immunofluorescent staining of herpes simplex virus antigen were analyzed. All 25 normal control subjects had negative reactions. All eight specimens from the lesions suspected of being herpes simplex keratitis showed positive reactions. Of the 48 specimens of lesions not suspected of being herpes simplex keratitis, 11 (23%) had positive reactions and 37 had negative reactions. Of the 11 eyes not suspected of having herpes simplex keratitis but with positive reactions on immunofluorescent staining, nine had recurrent erosions and the remaining two eyes had superficial punctate keratitis.

Corneal sensitivity was also determined in each group. Measurements for the 25 normal control subjects ranged from 15.9 to 24.9 mg/0.0129 mm^2. Of the eight eyes suspected of having herpes simplex keratitis, one had normal corneal sensitivity and seven had decreased corneal sensitivity. Of the 11 eyes not suspected of having herpes simplex keratitis, but with positive reactions on immunofluorescent staining, three had normal corneal sensitivity and eight had decreased sensitivity. Of the 37 eyes not suspected of having herpes simplex keratitis and with negative immunofluorescent reactions, 26 had normal corneal sensitivity and 11 had decreased sensitivity. Positive results on immunofluorescent staining were well correlated with decreased corneal sensitivity.

We treated 19 patients with positive reactions on immunofluorescent staining with instillation of acyclovir ointment. All corneal lesions resolved thereafter.

Discussion

In our study, all 25 normal corneas had negative reactions on immunofluorescent staining, and all eight patients suspected of having herpes simplex keratitis showed positive reactions. No specimens were unreadable. Thus, a good correlation was found between the clinical findings and results of immunofluorescent staining in our patients with typical herpes simplex keratitis. Of the 48 eyes not suspected of having herpes simplex keratitis, 11 (23%) had positive reactions on staining for the virus antigen. These 11 patients probably did have herpes simplex keratitis although it was not clinically diagnosed. Nine of those 11 eyes had recurrent erosions. The epithelial defects were oval, central, and had hazy surrounding edges. Superficial stromal opacities were sometimes observed, although the main lesions were located in the epithelium. No stromal abscess or hypopyon was observed.

Of the eight eyes suspected of having herpes simplex keratitis and with positive results on immunofluorescent staining, seven had decreased corneal sensitivity. Of the 11 eyes not suspected of having herpes simplex keratitis but with positive reactions on immunofluorescent staining, eight (73%) had decreased corneal sensitivity. Conversely, of the 37 eyes with negative reactions on immunofluorescent staining, 11 (30%) had decreased corneal sensitivity. Decreased corneal sensitivity may be useful in confirming the diagnosis of herpes simplex keratitis. In the usual office setting without a device, touching the cornea with a cotton swab would detect the decreased corneal sensitivity.

Polymerase chain reaction and new immunologic tests, such as Herpchek (Dupont, Wilmington, Delaware) and enzyme immunofiltration, have been recently advocated in detecting herpes simplex antigen from clinical ocular samples,[4] although not all ophthalmologists can use those tests routinely. We believe that immunofluorescent staining and the measurement of corneal sensitivity are useful in making the diagnosis of herpes simplex keratitis.

References

1. Norn, M. S.: Dendritic (herpetic) keratitis. Follow-up examination of corneal sensitivity. Acta Ophthalmol. 48:383, 1970.
2. Zaitseva, N. S., Muravieva, T. V., Vinogradova, V. L., Shubladze, A. K., Maevskaya, T. M., Kasparov, A. A., and Rzhechitskaya, O. V.: Comparative evaluation of methods for laboratory diagnosis of herpetic eye disease. Am. J. Ophthalmol. 75:997, 1973.
3. Collum, L. T. M., Mullaney, J., Hillery, M., Mullaney, P., and Lester, R.: Two laboratory methods for diagnosis of herpes simplex keratitis. Br. J. Ophthalmol. 71:742, 1987.
4. Kaye, S. B., Lynas, C., Patterson, A., Risk, J. M., McCarthy, K., and Hart, C. A.: Evidence for herpes simplex viral latency in the human cornea. Br. J. Ophthalmol. 75:195, 1991.

OPHTHALMIC MINIATURE

Pince-nez, and the lenses tinted just a hint of violet. It rested the eyes, he said. He pioneered tinted lenses in our city. Sometimes I asked him if he wasn't afraid the violet tint would look like an unhealthy shadow under his eyes, but he would chuck me under the chin (if we weren't in the street) and say they made him look passionate.

Robertson Davies, *Murther & Walking Spirits*
New York, Viking Penguin, 1991, p. 226

Pupillary Constriction During Forceful Eyelid Closure

Terry A. Cox, M.D., and Kathleen B. Digre, M.D.

Pupillary constriction during forceful eyelid closure was investigated in 30 normal subjects. The right eye of each subject was filmed with an infrared-sensitive television camera in darkness before, during, and after eyelid closure. Clinically detectable constrictions were found in nine of the 30 subjects (30%). No significant correlation was found between amplitude of constriction and age of subject or baseline pupillary diameter. Forceful eyelid closure should be considered as a technique to elicit pupillary constriction in patients with a poor near response, but many subjects will have no detectable constriction using this maneuver.

CLOSING THE EYELIDS has two different effects on the pupil. If the eyelids are closed during ambient illumination, the amount of light entering the eye will be diminished; reopening the eyes will then lead to a typical light response of the pupil, with a contraction after a latency of about 250 milliseconds. The amount of pupillary constriction will depend on the length of time that the eyelids were closed; longer intervals of eyelid closure result in more pupillary constriction. Using pupillometry, this pupillary reflex to darkness[1] can even be detected after normal blinks.

The second response of the pupil is constriction during forceful eyelid closure. This reflex has been given various eponymic names, including the Westphal-Piltz phenomenon and the Galassi-Gifford reflex,[2] but it was originally described by von Graefe in 1854.[3] It has been considered a manifestation of the near response.[4] We recorded pupillary constriction during forceful eyelid closure in normal subjects to predict its usefulness in the clinical assessment of patients with abnormal pupils.

Subjects and Methods

The 30 normal subjects studied included nine men and 21 women, aged 24 to 57 years (median, 41.5 years).

The pupil of the right eye was videotaped by using an infrared-sensitive television camera connected to a video recorder. An artificial pupil was photographed at the beginning of the recording to provide calibration. Pupillary sizes were measured on the screen of a video monitor during frame-by-frame playback of the video recording. Additionally, the videotape was viewed at normal speed to assess whether measured differences in pupillary diameter would be clinically detectable. In one subject with large pupillary constrictions we also recorded pupillary diameter with a television pupillometer (Applied Science Laboratories, Waltham, Massachusetts).

Subjects were asked to look at a dim, red, light-emitting diode placed 1.5 m from the eye. The room was otherwise as dark as possible, but the amount of stray light was enough to elicit a small pupillary response to light after eyelid opening in two subjects. Periods of forceful eyelid closure lasting seven seconds were alternated with seven-second intervals of relaxation until four satisfactory repetitions were obtained. In most cases the eyes deviated upward during eyelid closure. Pupillary measurements were made from the last video frame before eyelid closure and the first frame after the eyelids had reopened and the eyes had returned to the primary position.

The pupillary response to near was recorded and assessed qualitatively in room light.

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Increasing Short-term Fluctuation by Increasing the Intensity of the Fixation Aid During Perimetry

Avinoam B. Safran, M.D., Charles Bader, M.D., Periklis D. Brazitikos, M.D.,
Catherine de Weisse, and Dominique Désangles

An increase in short-term fluctuation is a clinically useful clue in the diagnosis of acquired disorders of the visual pathways. However, short-term fluctuation can also be increased in normal subjects by several factors. We found an increase in short-term fluctuation occurred in normal subjects when the visual field was tested using a bright fixation aid. Eight normal subjects underwent automated perimetry with the Octopus 2000R, in which the dimmest (12.5 candelas/m^2) and brightest (435 cd/m^2) available fixation aids were used. Mean short-term fluctuation values were 1.63 ± 0.27 dB with the dimmest aid, and were 2.65 ± 1.26 dB with the brightest aid. The difference was significant using the paired *t*-test ($P = .037$). Moreover, mean sensitivity was reduced from 35.67 ± 2.26 dB to 33.66 ± 1.71 dB when the brightest fixation aid was used ($P = .004$). In six of eight subjects, the relative changes in short-term fluctuation after an increase in brightness of the fixation aid were more pronounced than those in mean sensitivity. An increase in intensity of the fixation aid may cause visual changes in normal subjects that resemble those induced by disorders in the visual pathways. Whenever possible, minimal intensity of the fixation aid should be used to allow for an adequate interpretation of short-term fluctuation values.

IN AUTOMATED STATIC PERIMETRY, short-term fluctuation has been defined as the variation in threshold measurements during a visual field test.[1] In normal subjects, a limited amount of fluctuation occurs, which is mainly caused by the nature of the psychophysical measurement technique.[2] Short-term fluctuation in normal subjects has also been attributed to several other causes, including physiologic variation in the function of the retina and the optic nerve, learning effect, fatigue, and insufficient attention.[3,4] Marked increase in short-term fluctuation, however, is generally considered a sensitive clue to acquired disorders in the anterior visual pathways,[3-7] if the patient's reliability is good.[8] Increases in short-term fluctuation with otherwise normal visual fields have even shown a predictive value for visual field defects that were detected later.[9]

With sophisticated automated perimeters such as the Octopus, brightness of the fixation aid is adjustable. For routine use, minimal intensity is suggested, but in patients with marked alteration in the central field, a progressive increase in fixation aid brightness is advised until the patient perceives the fixation aid and achieves steady fixation. We observed an increase in short-term fluctuation in normal subjects undergoing perimetry when a bright fixation aid was used. Because of its clinical importance, we evaluated this phenomenon's reproducibility by testing a series of healthy subjects, using dim and bright fixation aids.

Subjects and Methods

Eight normal subjects, 21 to 45 years old (mean age, 35 years) were included in the study. All were familiar with Octopus perimetry. They underwent an examination of the centromacular (4.5-degree radius) area of the

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visual field by means of option 4 of the Octopus neuro-ophthalmologic program N1.[10] The Octopus 2000R was used, with a 5-degree radius fixation ring. Both short-term fluctuation and mean sensitivity[11] were determined. For each subject, the examination was performed twice: in one test, the dimmest fixation aid available with the Octopus 2000R was used; and in the other, the brightest one was used. The brightness of the fixation aids was 12.5 and 435 cd/m^2, respectively. In the first group of four subjects (Subjects 1 through 4), the procedure started with the dimmest fixation aid, whereas in the second group (Subjects 5 through 8) the brightest aid was used initially. The paired *t*-test was used to analyze the results.

Results

The reliability of the subjects was excellent, and no false response was recorded. After the increase in brightness of the fixation aid, short-term fluctuation increased in all but one subject. The mean sensitivity decreased in all but one subject. Both changes were statistically significant (Table). Decrease in mean sensitivity and increase in short-term fluctuation occurred whether the examination began with a bright fixation aid or a dim one. When the brightest fixation aid was used, the standard deviation of short-term fluctuation increased markedly (Table). In six of eight tested subjects, relative increase in short-term fluctuation (expressed in standard deviations of the mean value measured with the dim aid) was greater than relative decrease in mean sensitivity. Increase in short-term fluctuation was associated with a large change in standard deviation, indicating the effect of intensity of fixation aid on short-term fluctuation is relatively unpredictable across subjects.

Discussion

In automated perimetry, transient changes during a visual field test are expressed in short-term fluctuation values.[12] Because of the clinical importance of short-term fluctuation in examining the visual field,[3,6] recognizing the factors that influence this variable is mandatory. In our study, light intensity of the fixation aid was one such factor, as increase in intensity resulted in increase in short-term fluctuation.

The changes in short-term fluctuation that we observed after an increase in brightness of the fixation aid were marked. Although short-term fluctuation determinations made using a dim fixation aid were within the normal range, that is, less than 2 dB[1] (with the exception of one subject who showed 2.1 dB short-term fluctuation), values were greater than 2 dB in all but two subjects when the brighter fixation aid was used. The standard deviation of short-term fluctuation was also increased in normal subjects when the intensity of fixation aid was increased. The standard deviation/short-term fluctuation ratio increased by a factor of 2.9.

In our study, increase in short-term fluctuation might have been caused by transient changes in visual function or instability of fixation. Transient changes in the visual performance of normal subjects is well established.[12] Several mechanisms are probably involved, such as fluctuation in the functions of the retina and the optic nerve. Several observations support the involvement of retinal factors in the genesis of periodic visual changes, including rapid transient oscillations in the resting potential of the eye[13,14] and variability in the activity of the retinal ganglion cells in response to a given stimulus, a phenomenon that seems to be intrinsic to the retina.[15] Intermittent blocks in conduction of optic nerve axons could also account for physiologic fluctuations in vision, as the hyperpolarization after a train of action potentials may lead to a transient refractory period.[16,17] Other phenomena associated with transient changes in vision include repeated pauses in pupil responses to light-flash stimulation[18,19] and fluctuation in eye lens power.[12]

Increase in transient changes in vision might be related to an increase in intensity of the fixation aid, by mechanisms involving glare or increase in ambient illumination, or both. Increasing the intensity of fixation aid results in glare effects, which reduce contrast sensitivity.[20] Changes in vision related to this condition might also include an increase in short-term fluctuation. Furthermore, the disability glare induced by the fixation aid can be likened to that elicited by a veiling luminance, that is, a luminance added to both the background and the object.[20,21] Variability of threshold responses in automated static perimetry has recently been suggested to increase when background illumination is reduced from photopic to mesopic

TABLE
SHORT-TERM FLUCTUATION AND MEAN SENSITIVITY VALUES MEASURED USING EITHER A DIM OR A BRIGHT FIXATION AID

	SHORT-TERM FLUCTUATION (P = .037)*		MEAN SENSITIVITY (P = .004)*	
SUBJECT NO.	WITH DIM FIXATION AID	WITH BRIGHT FIXATION AID	WITH DIM FIXATION AID	WITH BRIGHT FIXATION AID
1	1.8	3.1	33.0	31.5
2	1.2	2.2	32.3	30.6
3	1.8	1.3	37.6	34.6
4	1.6	1.7	37.3	34.4
5	1.6	3.3	33.7	34.7
6	1.5	2.2	36.9	33.6
7	1.5	2.1	37.1	34.4
8	2.1	5.3	37.5	35.5
Mean ± SD	1.63 ± 0.27	2.65 ± 1.26	35.67 ± 2.26	33.66 ± 1.71

*As determined by the paired *t*-test.

range.[22] Comparison of these results with our own is difficult, however, as the range of illumination conditions in that study was different from the range used in our study.

Increase in short-term fluctuation might also result from increase of instability of fixation. Various mechanisms may be involved in this process, including alteration in visibility of the fixation aid caused by changes in local adaptation, and increase in gaze attraction to the eccentrically located fixation aid.

When a light-test spot is presented at a given eccentricity from the fixation point to a perfectly fixating observer, it becomes invisible after some 326e. This process is called local adaptation. Local adaptation time varies according to target blur, length of the boundaries,[23] eccentricity of the test spot from the fixation,[24] and other variables. With an eccentricity of 5 degrees (that is, eccentricity of the ring stimulus used in our study for fixation), local adaptation time is approximately 20 seconds.[24] Although the local adaptation phenomenon is known to occur whatever the brightness of the test spot,[25] the effect of degree of brightness of the spot has not been well studied, especially with regard to its position in the visual field. Increase in light intensity of the stimulus used as a fixation aid might influence time of changes in local adaptation, hence the perception of the aid, and consequently fixation steadiness. Light intensity could also affect other numerous motor (and therefore sensory) mechanisms involved in the fixation process,[26,27] possibly those related to the resurgence of visibility, which occurs after adaptation when location of the stimulus projection onto the retina is changed.

Finally, increase in light intensity of the fixation aid might alter the steadiness of fixation by enhancing the primitive reflex of shifting gaze toward stimuli at some distance from the fixation point, which is usually suppressed by mechanisms involving attention and the frontal lobes.[28]

In addition to the changes in short-term fluctuation, using brighter fixation aid of the stimulus resulted in decreased mean sensitivity, that is, an increase in the differential light threshold. An increase in differential light threshold might be related to that of background luminance, as an increase in background luminance has resulted in a global reduction of the visual capability by perimetry[29] and the flashing, repeat static test.[30] Furthermore, as already mentioned, increasing the intensity of the fixation aid in automated perimetry induces glare effects, which in turn reduce contrast sensitivity.[20] Therefore, the increase in the differential light threshold that we found with increase in intensity of the fixation aid was to be expected.

Interestingly, after the increase in brightness of the fixation aid, relative changes were more pronounced in short-term fluctuation than in mean sensitivity in six subjects, whereas the opposite was true in two subjects. Thus, in normal subjects, short-term fluctuation sometimes appeared to be a more sensitive indicator of the visual impairment resulting from an increase in background luminance than the simple measurement of differential light threshold. In affected patients too, threshold variability proved to be a more sensitive indicator of visual pathway damage than the usual measurement of mean differential light threshold; this was demonstrated with patients suffering from multiple sclerosis[31] and with patients suspected of having glaucoma.[9] Moreover, it was shown that vision variability in patients with multiple sclerosis increased with background luminance.[32] In abnormal conditions, such as demyelinating diseases, intermittent conduction blocks in the optic nerve after trains of action potentials may be expected to be frequent, and to be caused by a reduction in the safety factor associated with the loss of myelin.[32] Our findings suggest that a subtle alteration in visual function resulting from increase in light intensity of the fixation aid may resemble discrete changes induced by disorders in the anterior visual pathways.

References

1. Flammer, J., Drance, S. M., Augustiny, L., and Funkhouser, A.: Quantification of glaucomatous visual field defects with automated perimetry. Invest. Ophthalmol. Vis. Sci. 26:176, 1985.
2. Flammer, J.: Fluctuations in computerized perimetry. In Whalen, W. R., and Spaeth, G. L. (eds.): Computerized Visual Fields. What They Are and How to Use Them. Thorofare, New Jersey, Slack Incorporated, 1985, pp. 47–58.
3. Flammer, J., Drance, S. M., Fankhauser, F., and Augustiny, L.: Differential light threshold in automated static perimetry. Factors influencing short-term fluctuation. Arch. Ophthalmol. 102:876, 1984.
4. Augustiny, L., and Flammer, J.: The influence of artificially induced visual field defects on the visual field indices. In Heijl, A., and Greve, E. (eds.): Proceedings of the 6th International Visual Field Symposium. Dordrecht, The Netherlands, Dr. W. Junk Publishers, 1985, pp. 55–67.
5. Safran, A. B., and de Weisse, C.: Increase in short-term fluctuation maybe a clue for differentiating dystrophic from acquired defects in anterior visual pathways (correspondence). Arch. Ophthalmol. 107:16, 1989.
6. Werner, E. B., Petrig, B., Krupin, T., and Bishop, K. I.: Variability of automated visual fields in clinically stable glaucoma patients. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 1083.
7. Brazitikos, P. D., Safran, A. B., Simona, F., and Zulauf, M.: Threshold perimetry in tilted disk syndrome. Arch. Ophthalmol. 108:1698, 1990.
8. Flammer, J., Drance, S. M., and Zulauf, M.: Differential light threshold. Short- and long-term fluctuation in patients with glaucoma, normal controls, and patients with suspected glaucoma. Arch. Ophthalmol. 102:704, 1984.
9. Werner, E. B., and Drance, S. M.: Early visual field indices. Graefes Arch. Clin. Exp. Ophthalmol. 224:389, 1986.
10. Safran, A. B., and Mermoud, C.: Neuro-ophthalmological global analysis program developed on a personal computer and the Octopus 2000R. In Heijl, A. (ed.): Perimetric Update 1988/89. Amsterdam, The Netherlands, Kugler and Ghedini, 1989, pp. 151–155.
11. Flammer, J.: The concept of visual field indices. Graefes Arch. Clin. Exp. Ophthalmol. 224:389, 1986.
12. Ronchi, L., and Brancato, R.: Periodicities of visual responsiveness. Ophthalmologica 163:189, 1971.
13. Kris, C.: Diurnal variations in peri-orbitally measured eye potential level. Electroencephalogr. Clin. Neurophysiol. 9:382, 1957.
14. Arden, G., Kelsey, J. H., and Barrada, A.: New clinical test of retinal function based upon the standing potential of the eye. Br. J. Ophthalmol. 46:449, 1962.
15. Stone, J., and Fabian, M.: Summing potential of the cat's retinal ganglion cells. Vision Res. 8:1023, 1968.
16. Gasser, H. S.: Changes in nerve potential produced by rapidly repeated stimuli and their relation to the responsiveness of nerve stimulation. Am. J. Physiol. 111:35, 1935.
17. Bostock, H., and Grafe, P.: Activity dependent excitability changes in normal and demyelinated rat spinal root axons. J. Physiol. 365:239, 1985.
18. Lowenstein, O., and Friedman, E. D.: Pupillographic studies. I. Present state of pupillography; its method and diagnostic significance. Arch. Ophthalmol. 27:969, 1942.
19. Safran, A. B., Walser, A., Roth, A., and Gauthier, G.: Pupil cycle induction test. A way of evaluating the pupillary light reflex. Ophthalmologica 183:205, 1981.
20. Verriest, G., and Uvijls, A.: Disability glare in normal and diseased eyes. Clin. Vision Sci. 3:253, 1989.
21. Vos, J. J.: Disability glare. A state of the art report. CIE J. 3:39, 1984.
22. Crosswell, H. H., Stewart, W. C., Caiscairo, M. A., and Hunt, H. H.: The effect of background intensity on the components of fluctuation as determined by threshold-related automated perimetry. Graefes Arch. Clin. Exp. Ophthalmol. 229:119, 1991.
23. West, D. C.: Brightness discrimination with a stabilised image. Vision Res. 7:949, 1967.
24. Cibis, P.: Zur Pathologie der Lokaladaptation. I. Mitteilung. Graefes Arch. Klin. Exp. Ophthalmol. 148:1, 1948.

25. Yarbus, A. L.: Eye Movements and Vision. New York, Plenum Press, 1967, pp. 62–64.

26. Alpern, M.: Eye movements. In Jameson, D., and Hurvich, L. M. (eds.): Handbook of Sensory Physiology, vol. 7, pt. 4. Berlin, Springer-Verlag, 1972, pp. 304–325.

27. Kowler, E.: The role of visual and cognitive processes in the control of eye movement. In Kowler, E. (ed.): Eye Movements and Their Role in Visual and Cognitive Processes. Amsterdam, Elsevier, 1990, pp. 2–14.

28. Guitton, D., Buchtel, H. A., and Douglas, R. M.: Disturbances of voluntary saccadic eye movement mechanisms following discrete unilateral frontal lobe removals. In Lennerstrand, G., Zee, D. S., and Keller, E. L.(eds.): Functional Basis of Ocular Motility Disorders. Oxford, Pergamon Press, 1982, pp. 497–499.

29. Silverstone, D. E., and Hirsch, J.: Automated Visual Field Testing. East Norwalk, Connecticut, Appleton-Century-Crofts, 1986, p. 14.

30. Enoch, J. M., Fitzgerald, C. R., and Temme, L. A.: Remission of anomalies. An important aid to analysis. In Proenza, L. M., Enoch, J. M., and Jampolsky, A. (eds.): Clinical Applications of Visual Psychophysics. Cambridge, England, Cambridge University Press, 1981, pp. 198–233.

31. Patterson, V. H, Foster, D. H., and Heron, J. R.: Variability of visual threshold in multiple sclerosis. Effect of background luminance on frequency of seeing. Brain 103:139, 1980.

32. Waxman, S. G.: Clinicopathological correlations in multiple sclerosis and related diseases. Adv. Neurol. 31:169, 1981.

OPHTHALMIC MINIATURE

When I stopped in, my father was tending to his last patients of the day. "Better or worse?" he'd say. I could hear him through the closed door of his darkened examination room as he adjusted lenses and changed focal lengths. He clicked the lenses into place on the metal frames. "Better or worse?" Click, click. "Better or worse?" Click, click. By noon the patients were gone. Then, having asked enough questions for one day, my father would drive me cheerfully home for Saturday lunch without saying a word.

David Macfarlane, *Come by Chance*
New York, Poseiden, 1991, pp. 6-7

PERSPECTIVES

Controversies in the Management of Retinopathy of Prematurity

Paul Sternberg, Jr., M.D., Pedro F. Lopez, M.D., H. Michael Lambert, M.D.,
Thomas M. Aaberg, M.D., and Antonio Capone, M.D.

In 1942 and 1943, Terry[1,2] first identified the correlation between premature delivery and the development of retinal detachment associated with retrolental fibrovascular tissue formation. His description of retrolental fibroplasia was renamed retinopathy of prematurity in the 1980s, when it was recognized that many premature infants developed retinal vascular abnormalities that did not progress to total retinal detachment.[3-6]

Reports published in the 1950s described the possible relationship between the administration of increased amounts of oxygen and the development of retinopathy of prematurity.[7-9] This recognition led to rigid curtailment in the use of oxygen and a marked decrease in the incidence of retinopathy of prematurity. However, this procedure may have caused an increase in the number of premature infant deaths from respiratory distress syndrome, which was later shown to be related to oxygen deprivation.[10,11]

Since the 1980s, many advances in neonatology, including the development of continuous arterial oxygen monitoring, have occurred.[12-14] This has led to a marked increase in the survival of low-birthweight infants, but has also led to an increase in the number of children with retinopathy of prematurity.[14,15] The new epidemic of retinopathy of prematurity stimulated a resurgence of interest in the disease, resulting in more research into its pathogenesis, a reclassification of the disease, better guidelines for infant screening, and a search for new treatment modalities.[5,6,12,15-24]

On the basis of a cluster of pilot studies in the United States, Japan, and elsewhere, the Cryotherapy for Retinopathy of Prematurity Study was instituted in 1985.[21] In this study, infants with threshold disease (defined as five contiguous clock hours or eight noncontiguous clock hours of extraretinal neovascularization [Stage 3 disease] in Zone 1 or Zone 2 with associated posterior retinal vascular dilation and tortuosity [plus disease]) were randomly assigned to confluent cryoablation of the peripheral avascular retina.[21,25,26] At three months, the study group reported that cryotherapy significantly lowered the incidence of an unfavorable outcome from 51.4% in control eyes to 31.1% in treated eyes.[25] At 12 months, the results were similar with an unfavorable outcome in 47.4% of control eyes vs 25.7% of treated eyes.[26]

On the basis of the Cryotherapy for Retinopathy of Prematurity Study results, cryotherapy is now recommended for all infants with threshold disease.[21,25,26] However, a number of important questions remain about the management of this disease.

If both eyes are at threshold, should only one eye be treated?—The question of treating one or both eyes is more complex than it initially appears. It seems logical that if cryotherapy is beneficial for one eye, it should be beneficial for the other. However, because the disease resolves in half of the untreated eyes, and treatment fails in one fourth of the treated eyes, the analysis for the fellow eye becomes difficult. The question becomes even more confusing when other presently unknown aspects of treatment are taken into account (the effect of treatment on long-term visual acuity outcome or the risk of late retinal detachment incurred by an eye after cryotherapy, for example).

The Cryotherapy for Retinopathy of Prematurity Study Group advocates treatment of only one eye if the child has bilateral symmetric Zone 2 disease, but advocates treatment of both eyes if the disease is in Zone 1.[5,25,26] Caution in advocating treatment of the second eye in Zone 2 threshold retinopathy of prematurity reflects concern regarding the potential incidence of severe adverse long-term treatment sequelae in a disease that has over a 50% spontaneous regression rate. No such reservations exist with regard to the relative risk of treatment vs observation in Zone 1 threshold retinopathy of prematurity. In this disease, the visual risks of cryotherapy are clearly outweighed by an overwhelmingly poor natural course of diseases, in which the treatment outcome of 95% of eyes is unfavorable.[25,26] However, unlike Zone 2 disease, the benefits of cryotherapy for Zone 1 threshold retinopathy of prematurity are uncertain. Treatment failed after one year in 75% of eyes that underwent cryotherapy as compared with the failûre of treatment of 95% of eyes in the observation group.[26] As underscored by Hindle,[27] the treatment benefit of cryotherapy for Zone 1 disease was not statistically different from observation alone. Although it may be argued that a small sample size in each group prevented statistical significance,[27] the treatment effect was hardly dramatic.

The lack of a clear substantive treatment benefit has caused some to question the value of cryotherapy for the second eye in Zone 1 threshold retinopathy of prematurity.[28] However, until a more effective treatment is identified, the potential, although small, for improved outcome after cryotherapy may outweigh the relatively small visual and systemic risks of treatment. A complex bayesian mathematical model has been developed by Phelps and Phelps[28] to study the issue of treating one or both eyes.

Perhaps the principal reservation in advocating universal treatment of the second eye in bilateral Zone 2 retinopathy of prematurity is the issue of the long-term consequences of treatment. In this regard, the main concern is the incidence of late-onset retinal detachment. This has recently been reported by Greven and Tasman[29] in three infants, aged 15 months to 4 years, who developed retinal detachment one to four years after cryotherapy for threshold retinopathy of prematurity. More detachments will likely be reported as cryotherapy is performed more frequently and as the children grow older.

However, rhegmatogenous retinal detachments often develop in adults with spontaneously regressed retinopathy of prematurity. Additionally, the ability to achieve anatomic success in these eyes is much greater than it is in eyes with Stage 5 retinopathy of prematurity detachments.[29-31] Moreover, the poor visual success rate after surgical repair of Stage 5 retinal detachments as compared with later-onset, retinopathy of prematurity-related, retinal detachments suggests the latter to be preferable. However, the critical issue is the incidence of this late complication, which currently appears to be uncommon.[29]

We are presently recommending cryotherapy when an eye reaches threshold, regardless of the status of the contralateral eye. If both eyes reach threshold, both eyes receive cryotherapy. If one eye suffers a rhegmatogenous retinal detachment, surgical repair is attempted, with the knowledge that the prognosis for this eye is better than it would have been if it were a Stage 5 retinal detachment.

How should one manage an eye that does not show regression after cryotherapy?—Most eyes will respond rapidly to cryotherapy after seven to ten days of treatment. These eyes will show less dilation and tortuosity of the posterior retinal vessels, a decrease in the vascular engorgement of the mesenchymal ridge, and a diminution in the degree and extent of the neovascularization. When no response to treatment has been noticed, but the eye has not progressed past Stage 3, the periphery should be examined carefully to assess the confluence of cryotherapy. Large areas devoid of cryoscarring, caused by the difficulty in performing the treatment because of poor pupillary dilation, vitreous haze, or surgeon inexperience, can often be identified. In these cases, retreatment with supplemental cryotherapy to the untreated areas can be beneficial, similar to the way supplemental photocoagulation is implemented in diabetic eyes with neovascularization that has not regressed after initial scatter treatment.

If the eye develops a peripheral retinal detachment, the examiner must decide whether it is an exudative or tractional detachment. An exudative detachment may delay the effect of the cryotherapy until the subretinal fluid has resolved. A tractional detachment indicates that the eye has progressed to Stage 4 and that cryotherapy has probably failed.

Should cryotherapy be performed with the patient under local or general anesthesia?—Because of the tenuous physical condition of many premature infants, resistance to the use of general anesthesia for cryotherapy may be considerable. In the Cryotherapy for Retinopathy of Prematurity Study, general anesthesia was used in only 27.5% of the cases.[25] Systemic complications of anesthesia included bradycardia, cyanosis, as well as tachycardia, seizure, and transient blood pressure changes. The authors of the report do not state whether these were more common in the generally or locally anesthetized group, although the type of anesthesia selected did not affect the outcome of the treatment.

If possible, we recommend performing cryotherapy in the nursery with the neonatologist present, using subconjunctival lidocaine. If incisional cryotherapy is required, we would likely recommend the use of general anesthesia. If both eyes were being treated at one setting, we would likely recommend general anesthesia. However, all decisions regarding anesthesia are done in close consultation with the infant's neonatologist.

How should Zone 1 disease be managed?—The Cryotherapy for Retinopathy of Prematurity Study identified Zone 1 disease as having a considerably worse prognosis than threshold disease in Zone 2.[26] Cryotherapy treatment of 75% of the Zone 1 eyes failed; these dismal results are tempered only somewhat by the 91.7% failure rate in the control group.

The Cryotherapy for Retinopathy of Prematurity Study Group responded to these findings by advocating bilateral cryotherapy for symmetric Zone 1 disease. However, an equally acceptable interpretation of these data would suggest that the technique of treatment advocated in this study that proved to be so effective for Zone 2 disease is not appropriate for Zone 1 disease. It is possible that the extensive amount of cryotherapy required in these eyes causes contraction of the vitreous gel or vascular leakage, or both, and results in subsequent retinal detachment. Scattering the cryotherapy or dividing the treatment into several sessions would possibly be advantageous in this regard. However, division of the treatment into several sessions entails additional anesthesia risk and logistical costs.

Perhaps the definition of threshold retinopathy of prematurity for Zone 1 and Zone 2 should differ to allow earlier intervention in the more severe Zone 1 disease. This new definition of Zone 1 threshold retinopathy of prematurity might, for example, be predicated on the amount of Zone 1 retinopathy of prematurity that results in a 50% unfavorable outcome in this subgroup, rather than the 91.7% level occurring with the current definition. This, however, will require a better understanding of the natural course of Zone 1 retinopathy of prematurity.

What is the role of photocoagulation in the treatment of retinopathy of prematurity?—The principles underlying the positive effect of cryotherapy for retinopathy of prematurity revolve around the destruction of the avascular peripheral retina. Theoretically, photocoagulation is also capable of panretinal ablation, but until recently, there was not a delivery system that could do so as easily as cryotherapy.[22,31-33] However, the development of the laser indirect ophthalmoscope now allows the use of photocoagulation. Several pilot studies have shown it to have a comparable positive effect on threshold disease.[22,31,32] Laser photocoagulation of the peripheral retina may be advantageous in the following ways: (1) by limiting the damage to adjacent structures caused by cryotherapy; (2) by lessening the inflammation and vitreous contraction stimulated by cryotherapy; (3) by decreasing serious ocular and systemic complications that result from the greater manipulation required for cryotherapy, such as intraocular hemorrhage and bradycardia; and (4) by being technically less cumbersome, particularly with the new diode laser. Additionally, laser photocoagulation may be particularly advantageous in treatment of postequatorial retina in Zone 1 retinopathy of prematurity. The disadvantages of laser photocoagulation primarily reflect the need for adequate pupillary dilation and clear media, conditions that may be compromised in the advanced stages of retinopathy of prematurity.

A multicenter collaborative trial has demonstrated the benefit of cryotherapy. However, treatment failed in 25% of the treated eyes, particularly those with Zone 1 disease, the group that may benefit most from photocoagulation. Although the use of photocoagulation has been criticized from a medicolegal risk perspective because its benefit has not been proven, the Japanese reported the use of xenon arc photocoagulation for retinopathy of prematurity in the 1960s.[34] More recently, McNamara and colleagues[35] demonstrated no difference in the outcome between laser treatment and cryotherapy in a series of 22 infants who were randomly assigned to the two treatment modalities.[35] We welcome the investigation of laser photocoagulation treatment for threshold retinopathy of prematurity, particularly for Zone 1 disease.

The demonstration of the efficacy of cryotherapy in the management of retinopathy of prematurity represents a tremendous breakthrough, particularly because of the increasing number of surviving low-birthweight infants. The questions that have been discussed in this study have been practical, but many more questions remain, including whether or not cryotherapy would be more beneficial if the definition of threshold were modified. Furthermore, it would be helpful to determine the features of eyes that regressed without treatment and the proper management of Stage 4 eyes.

The recent publication of dismal visual results for children undergoing vitrectomy for Stage 5 retinopathy of prematurity reinforces the importance of the results of the Cryotherapy for Retinopathy of Prematurity Study.[31] Furthermore, it emphasizes the need for compulsory infant screening programs. Great advances have been made in the treatment of this disease, but many questions await answering.

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References

1. Terry, T. L.: Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report. Am. J. Ophthalmol. 25:203, 1942.

2. ———: Fibroblastic overgrowth of persistent tunica vasculosa lentis in premature infants. II. Report of cases, clinical aspects. Arch. Ophthalmol. 29:36, 1943.

3. Flynn, J. T.: Acute proliferative retrolental fibroplasia. Evolution of the lesion. Graefes Arch. Klin. Exp. Ophthalmol. 195:101, 1975.

4. Flynn, J. T., O'Grady, G. E., Herrera, J., Kushner, B. J., Cantalino, S., and Milam, W.: Retrolental fibroplasia. I. Clinical observations. Arch. Ophthalmol. 95:217, 1977.

5. Committee for the Classification of Retinopathy of Prematurity: An international classification of retinopathy of prematurity. Arch. Ophthalmol. 102:1130, 1984.

6. Flynn, J. T., Bancalari, E., Bachynski, B. N., Buckley, E. B., Bawol, R., Goldberg, R., Cassady, J., Schiffman, J., Feuer, W., Gillings, D., Sim, E., and Roberts, J.: Retinopathy of prematurity. Diagnosis, severity and natural history. Ophthalmology 94:620, 1987.

7. Patz, A., Hoeck, L. E., and De La Cruz, E.: Studies on the effect of high oxygen administration in retrolental fibroplasia. I. Nursery observations. Am. J. Ophthalmol. 35:1248, 1952.

8. Campbell, K.: Intensive oxygen therapy as a possible cause of retrolental fibroplasia. A clinical approach. Med. J. Aust. 2:48, 1951.

9. Lanman, J. T., Guy, L. P., and Dancis, J.: Retrolental fibroplasia and oxygen therapy. JAMA 155:223, 1954.

10. Avery, M. E., and Oppenheimer, E. H.: Recent increase in mortality from hyaline membrane disease. J. Pediatr. 57:553, 1960.

11. McDonald, A. D.: Cerebral palsy in children of very low birth weight. Arch. Dis. Child. 38:579, 1963.

12. Flynn, J. T., Bancalari, E., Bawol, R., Goldberg, R., Cassaday, J., Schiffman, J., Feuer, W., Roberts, J., Gillings, D., Sim, E., Buckley, E., and Bachynski, B. N.: Retinopathy of prematurity. A randomized prospective trial of transcutaneous oxygen monitoring. Ophthalmology 94:630, 1987.

13. Hammer, M. E., Mullen, P. W., Ferguson, J. G., Pai, S., Cosby, C., and Jackson, K. L.: Logistic analysis of risk factors in acute retinopathy of prematurity. Am. J. Ophthalmol. 102:1, 1986.

14. Shohat, M., Reisner, S. H., Krikler, R., Nissenkorn, I., Yassur, Y., and Ben-Sira, I.: Retinopathy of prematurity. Incidence and risk factors. Pediatrics 72:159, 1983.

15. Phelps, D. L.: Retinopathy of prematurity. An estimate of vision loss in the United States—1979. Pediatrics 67:924, 1981.

16.. Hittner, H. M., Godio, L. B., Speer, M. E., Rudolph, A. J., Taylor, M. M., Blifeld, C., and Kretzer, F. L.: Retrolental fibroplasia. Further clinical evidence and ultrastructural support for efficacy of vitamin E in the preterm infant. Pediatrics 71:423, 1983.

17. Kretzer, F. L., Mehta, R. S., Johnson, A. T., Hunter, D. G., Brown, E. S., and Hittner, H. M.: Vitamin E protects against retinopathy of prematurity through action on spindle cells. Nature 309:793, 1984.

18. Ben-Sira, I., Nissenkorn, I., and Kremer, I.: Retinopathy of prematurity. Surv. Ophthalmol. 33:1, 1988.

19. Foos, R. Y.: Retinopathy of prematurity. Pathologic correlation of clinical stages. Retina 7:260, 1987.

20. Palmer, E. A.: Optimal timing of examination for acute retrolental fibroplasia. Ophthalmology 88:662, 1981.

21. Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Arch. Ophthalmol. 106:471, 1988.

22. Majima, A., Takahashi, M., and Hibino, Y.: Clinical observations of photocoagulation on retinopathy of prematurity. Jpn. J. Clin. Ophthalmol. 30:93, 1976.

23. McPherson, A., and Hittner, H. M.: Scleral buckling in 2½ to 11-month-old premature infants

with retinal detachment associated with acute retrolental fibroplasia. Ophthalmology 86:819, 1979.

24. Chong, L. P., Machemer, R., and de Juan, E.: Vitrectomy for advanced stages of retinopathy of prematurity. Am. J. Ophthalmol. 102:710, 1986.

25. Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity. Three-month outcome. Arch. Ophthalmol. 108:195, 1990.

26. Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome—structure and function. Arch. Ophthalmol. 108:1408, 1990.

27. Hindle, N. W.: Cryotherapy for retinopathy of prematurity. None, one or both eyes. Arch. Ophthalmol. 108:1375, 1990.

28. Phelps, D. L., and Phelps, C. E.: Cryotherapy in infants with retinopathy of prematurity. A decision model for treating one or both eyes. JAMA 261:1751, 1989.

29. Greven, C. M., and Tasman, W.: Rhegmatogenous retinal detachment following cryotherapy in retinopathy of prematurity. Arch. Ophthalmol. 107:1017, 1989.

30. Trotta, F., Sanders, R. J., and Hirose, T.: Outcome of vitreoretinal surgery for retinal detachments in regressed retinopathy of prematurity. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 1145.

31. Quinn, G. E., Dobson, V., Barr, C. C., Davis, B. R., Flynn, J. T., Palmer, E. A., Robertson, J., and Trese, M. T.: Visual acuity in infants after vitrectomy for severe retinopathy of prematurity. Ophthalmology 98:5, 1991.

32. Landers, M. B., III, Semple, H. C., Ruben, J. B., and Serdahl, G.: Argon laser photocoagulation for advanced retinopathy of prematurity. Am. J. Ophthalmol. 10:429, 1991.

33. Nissenkorn, I., Kremer, I., Gilad, E., Cohen, S., and Ben-Sira, I.: "Rush" type retinopathy of prematurity. Report of three cases. Br. J. Ophthalmol. 71:559, 1987.

34. Nagata, M., Kobayashi, Y., Fukada, H., and Suekane, K.: Photocoagulation for the treatment of retinopathy of prematurity. Jpn. J. Clin. Ophthalmol. 24:419, 1968.

35. McNamara, J. A., Tasman, W., Brown, G. C., and Federman, J. L.: Laser photocoagulation for Stage 3+ retinopathy of prematurity. Ophthalmology 98:576, 1991.

LETTERS TO THE JOURNAL

Frosted Branch Angiitis in a Patient With the Acquired Immunodeficiency Syndrome

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Frosted branch angiitis of the retina was first described in a 6-year-old boy in 1976 by Ito and associates.[1] The development of a severe sheathing along the retinal veins created the appearance of frosted tree branches, which prompted the name "frosted branch angiitis" for this peculiar form of acute retinal vasculitis. Recently two cases of unilateral frosted branch angiitis were reported in North America.[2] Little is known about the cause of this disease. In all previously reported cases, no underlying systemic disease or infection has been found.

The characteristic features of frosted branch angiitis can be summarized as follows: (1) severe sheathing of the retinal vessels appearing like frosted branches of a tree; (2) acute visual disturbance associated with signs of vitreous and anterior chamber inflammation; (3) fundus fluorescein angiography that shows no occlusion or stasis of the sheathed vessels; (4) fluorescein leakage from the sheathed vessels occurring in the later stages of angiography; (5) otherwise healthy patients; and (6) prompt response to corticosteroids.

We encountered a case with the typical clinical appearance of unilateral frosted branch angiitis in a patient with acquired immunodeficiency syndrome, cytomegalovirus retinitis, and cerebral toxoplasmosis.

A 49-year-old man was referred to our hospital because of a one-week history of decreased and blurred vision in the right eye. He tested positive for human immunodeficiency virus (HIV) in 1985, and cerebral toxoplasmosis was diagnosed in 1989. On initial examination, visual acuity was R.E.: 20/40 and L.E.: 20/20. The intraocular pressures were within normal limits. Filiform keratic precipitates, a moderate flare in the anterior chamber, and a slightly hazy vitreous were seen in the right eye. Biomicroscopic examination disclosed that the left eye was normal. Ophthalmoscopic examination of the right eye disclosed severe sheathing along the retinal veins with special emphasis on the posterior pole (Fig. 1). In the inferior fundus periphery, a tongue-shaped retinopathy with central necrosis and a hemorrhagic, yellow margin was seen. The left eye showed no evidence of inflammation or retinal microvasculopathy.

Fundus fluorescein angiography was performed at the initial examination. An early phase angiogram of the right eye disclosed a discrete microvasculopathy superior and nasal to the fovea. No leakage occurred along the

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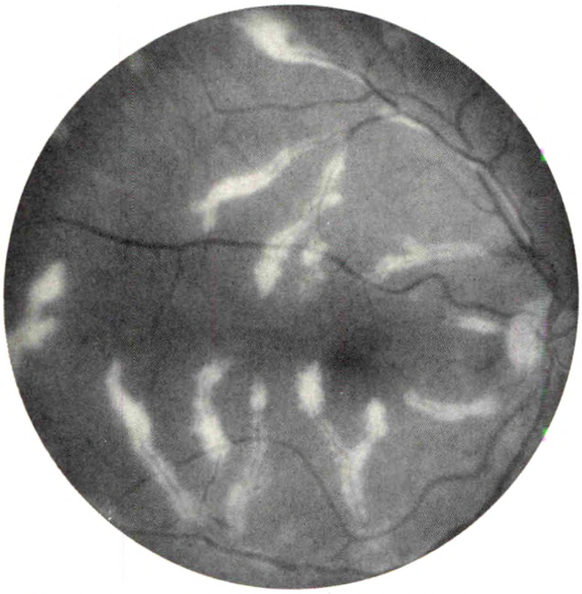

Fig. 1 (Geier and associates). Initial fundus examination of the right eye showing sheathing along the retinal veins with special emphasis on the posterior pole.

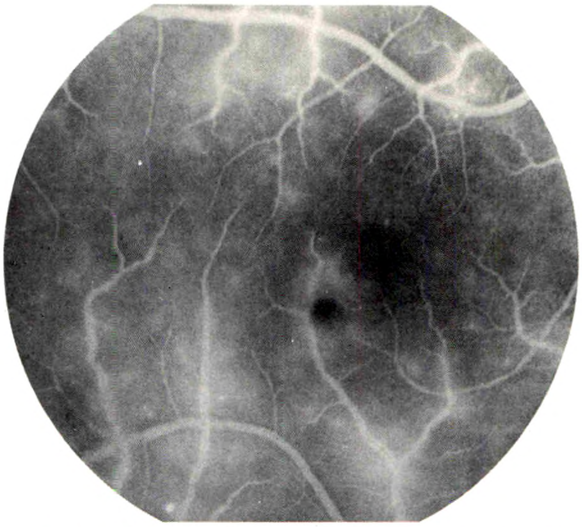

Fig. 2 (Geier and associates). Late phase fundus fluorescein angiogram of the right eye showing pronounced leakage from inflamed vessels of the posterior pole. No occlusion or stasis can be seen.

retinal veins. However, in the late phase angiogram an optic disk edema developed accompanied by pronounced leakage from most, but not all, of the inflamed vessels of the posterior pole (Fig. 2). No occlusion or stasis was found. No leaking vessels or papilledema could be detected in the left eye. The diagnosis of cytomegalovirus retinitis and frosted branch like angiitis of the right eye was made. The patient was given ganciclovir intravenously, 10 mg/kg of body weight per day.

Five days later the patient's visual acuity had decreased in the right eye to 20/200. Treatment with oral Fluocortolone (100 mg/day) was started. After two weeks sheathing disappeared and cytomegalovirus retinitis showed regression. Visual acuity in the right eye improved to 20/30. Fluocortolone was decreased stepwise to 20 mg/day and ganciclovir to 6 mg/kg of body weight per day.

Retinal periphlebitis has been reported in association with cytomegalovirus retinitis,[3] HIV infection,[4] and other infectious and systemic diseases including syphilis, tuberculosis, adenovirus infection, human T-cell lymphotropic virus type I infection, multiple sclerosis, sarcoidosis, and Crohn's disease. Severe retinal periphlebitis, as described here, is unique in cytomegalovirus retinitis and HIV infection. Differential diagnosis includes peripheral uveitis, Eales' disease, and acute retinal necrosis (Kirisawa-type uveitis and bilateral acute retinal necrosis), the latter showing severe obliteration of the retinal capillaries and vessels.

The adjunctive treatment with corticosteroids in patients with AIDS was expected to be beneficial in our patient. Corticosteroid-related development of Kaposi's sarcoma in AIDS patients has been reported but beneficial effects of corticosteroid therapy have been reported for *Pneumocystis carinii* pneumonia,[5] HIV-related immune thrombocytopenia, toxoplasmosis-induced cerebral edema, and severe HIV-associated myositis.

The periphlebitis in our patient met five of the six previously mentioned criteria for diagnosis of frosted branch angiitis: the patient had sheathing of retinal veins and mild anterior chamber and vitreous involvement (criteria 1 and 2), fluorescein angiography showed no occlusion or stasis and leakage occurred in the later stages (criteria 3 and 4), and response to corticosteroids was prompt (criterion 6). Only criterion 5 was not met because the patient suffered from AIDS, cytomegalovirus retinitis, and toxoplasmosis.

References

1. Ito, Y., Nakano, M., Kyu, N., and Takeuchi, M.: Frosted branch angiitis in a child. Jpn. J. Clin. Ophthalmol. 30:797, 1976.

2. Sugin, S. L., Henderly, D. E., Friedman, S. M., Jampol, L. M., and Doyle, J. M.: Unilateral frosted branch angiitis. Am. J. Ophthalmol. 111:682, 1991.

3. Kestelyn, P., Lepage, P., and Van de Perre, P.: Perivasculitis of the retinal vessels as an important sign in children with AIDS-related complex. Am. J. Ophthalmol. 100:614, 1986.

4. Culbertson, W. W.: Infections of the retina in AIDS. Int. Ophthalmol. Clin. 29:108, 1989.

5. The National Institutes of Health–University of California Expert Panel for Corticosteroids as Adjunctive Therapy for *Pneumocystis* Pneumónia: Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. N. Engl. J. Med. 323:1500, 1990.

Treatment of Endogenous Fungal Endophthalmitis With Systemic Fluconazole With or Without Vitrectomy

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Fungal infections are an increasing problem, particularly in immunocompromised patients, because the diagnostic and treatment processes of fungal infections may be difficult. Sensitivity measurements in vitro may not correspond to the clinical effects of treatment in vivo, and most of the drugs available are toxic and difficult to use.

In the treatment of *Candida* endophthalmitis, amphotericin B is considered to be the most effective agent but it should be used intraocularly. Amphotericin B can be administered by intravenous route but, according to Barrie,[1] it does not penetrate into the vitreous. It is also highly toxic when given intravenously. Flucytosine (5-fluorocytosine) may also be effective but resistance to this drug by *Candida* organisms may be a problem.

Of the new azole derivatives, fluconazole has a good antifungal activity in vitro. It is water-soluble, and 10% to 20% will be bound to plasma proteins. Therefore, the distribution of fluconazole in the organism is wide, and the penetration into the eye is good.[2,3] Additionally, fluconazole is easily absorbed after oral administration, it is excreted renally, and it has a long half-life and low toxicity. Thus, theoretically, fluconazole should be a welcome antifungal agent in ophthalmic use. The information on its effectiveness in endophthalmitis is scarce.[4,5]

Our patient was a 63-year-old man who had carcinoma of the rectum with abdominal and lung metastasis. He had had an abdominal operation with gut perforation, which led to broad spectrum antibiotic medication, and he was on a regimen of chemotherapy (5-fluorouracil). He developed *Candida* stomatitis, but other manifestations of fungal infection had not been diagnosed.

Ophthalmic examination was carried out because of blurred vision in the patient's right eye. The visual acuity was 20/50, there were cells in the anterior chamber, and diffuse haze and cells in the vitreous. A fairly dense, white infiltrate was observed on the right optic disk (Fig. 1, left).

The left eye was amblyopic, and visual acuity was 20/60. The anterior chamber was not inflamed, but there were also cells in the vitreous, and an active white vitreoretinal lesion was observed in the midperiphery (Fig. 1, right).

On the basis of the history of malignancy and chemotherapy as well as previously diagnosed *C. albicans* stomatitis and the fundus lesions, the diagnosis of fungal endophthalmitis was proposed. In the vitreous sample of the right eye, yeast spots were observed on microscopy. The bacterial culture was negative.

Following vitreous tap, 5 μg of amphotericin B was injected intravitreally. Because of more intense inflammatory signs in both the anterior chamber and vitreous, pars plana vitrectomy was performed three days later followed again by 5 μg of amphotericin B intravitreally. In the left eye, no treatment was given locally.

At the time of the first vitreous tap systemic treatment with fluconazole was started. Because of renal insufficiency, the treatment was given every second day, initially with 200 mg of fluconazole intravenously during the first two weeks. From the third week the daily dose was 300 mg of fluconazole orally for another six weeks. The treatment was well tolerated without any side effects.

After four months of follow-up the eyes were symptom-free and the vision had improved. The visual acuity was 20/30 in the right eye. In the left amblyopic eye, the visual acuity was

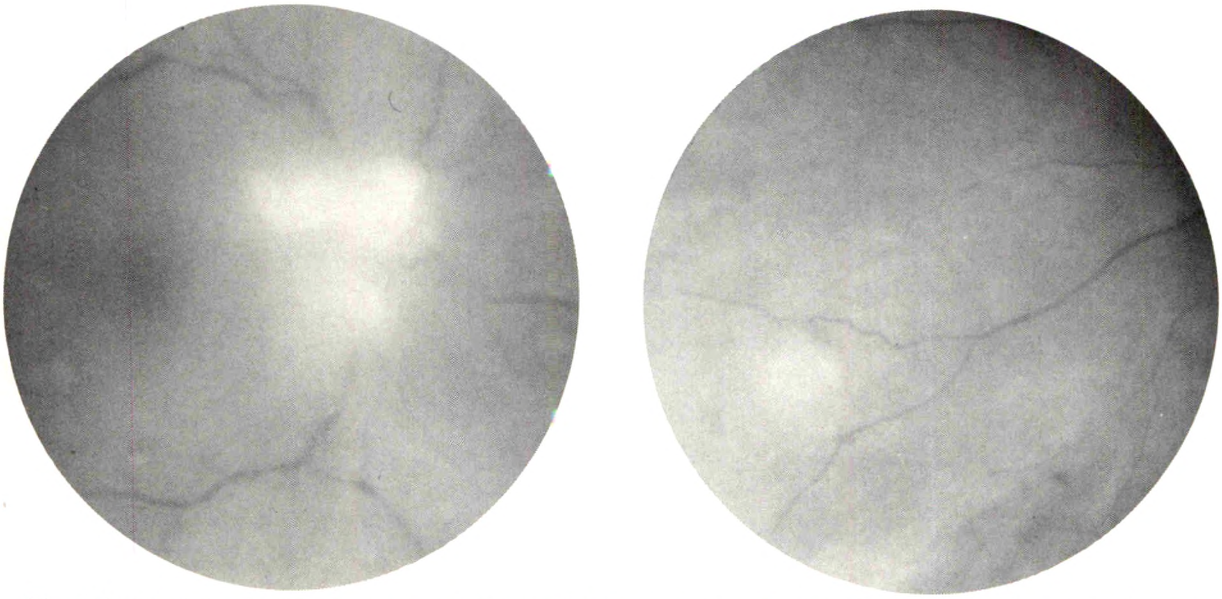

Fig. 1 (Laatikainen, Tuominen, and von Dickhoff). Fundus lesions in the right (left) and the left (right) eyes before treatment.

unchanged at 20/60. The anterior chamber was not inflamed, the vitreous was clear in both eyes, and no retinal infiltrates were seen (Fig. 2).

The right eye of this patient had both vitrectomy and amphotericin B intravitreally. Thus, it is difficult to determine whether systemic use of fluconazole had any effect on this eye. In the left eye no treatment was given locally, and the only treatment was systemic fluconazole but the inflammatory changes cleared completely.

Depending on the severity of the infection, we suggest that fluconazole may be considered in fungal endophthalmitis for systemic, usually oral, treatment either alone for mild cases, or in combination with intravitreous amphotericin B

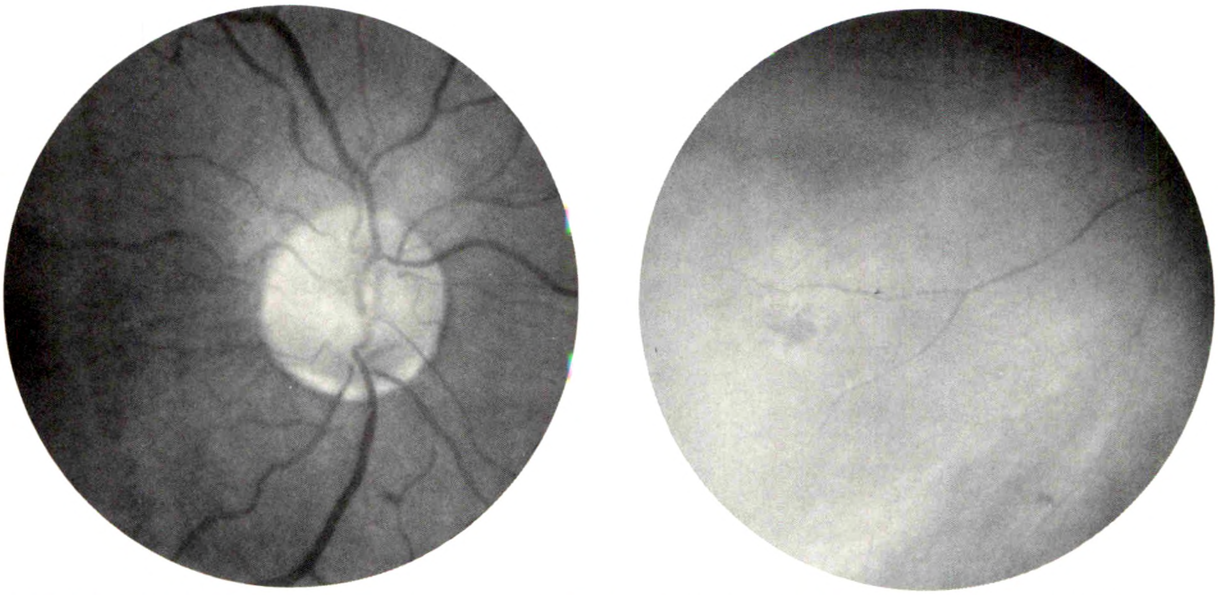

Fig. 2 (Laatikainen, Tuominen, and von Dickhoff). Fundus appearance of the right (left) and the left (right) eyes after four months of follow-up.

in more severe cases with or without vitrectomy. If this drug proves to be effective, it would be markedly less toxic than most other antifungal agents available.

References

1. Barrie, T.: The place of elective vitrectomy in the management of patients with *Candida* endophthalmitis. Graefes Arch. Clin. Exp. Ophthalmol. 225:107, 1987.
2. Savani, D., Perfect, J., Cobo, M., and Durack, D.: Penetration of new azole compounds into the eye and efficacy in experimental *Candida* endophthalmitis. Antimicrob. Agents Chemother. 31:6, 1987.
3. O'Day, D. M., Foulds, G., Williams, T. E., Robinson, R. D., Allen, R. H., and Head, W. S.: Ocular uptake of fluconazole following oral administration. Arch. Ophthalmol. 108:1006, 1990.
4. Despres, E., Weber, M., Jouart, D., Sahel, J., and Flament, J.: Uvéo-papillite á candida albicans. Discussion diagnostique et thérapeutique á propos d'une observation. Bull. Soc. Ophtalmol. Fr. 90:105, 1990.
5. Brod, R. D., and Flynn, H. W., Jr.: Advances in the diagnosis and treatment of infectious endophthalmitis. Curr. Opin. Ophthalmol. 2:306, 1991.

Aqueous Flare in Eyes With Choroidal Malignant Melanoma

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The laser flare-cell meter was developed to quantify aqueous flare and cells by analyzing anterior chamber laser beam scatter in vivo.[1] It has been shown[1,2] to yield sensitive and reproducible measurements. Clinical studies with this instrument have so far mainly focused on inflammatory[3] and postoperative[4] ocular changes. We investigated the applicability of the method to eyes with choroidal malignant melanoma.

We used the laser flare-cell meter (FC 1000, Kowa Co., Ltd., Tokyo, Japan) that was standardized with graded series of human albumin solutions. Flare values were determined after pupillary dilation with 0.5% tropicamide and 5% phenylephrine hydrochloride and were converted into albumin concentration equivalents (milligrams per milliliter). Eleven eyes of 11 patients with choroidal malignant melanoma (six men and five women, age 56.0 ± 17.3 years), nine clinically unaffected fellow eyes, and 11 healthy eyes of 11 randomly selected age- and gender-matched control patients (six men and five women, age 56.6 ± 15.7 years) were examined. Diagnosis of malignant melanoma was based on characteristic clinical findings and confirmed histopathologically in five eyes that were enucleated. Maximal tumor prominence as measured by A-scan ultrasonography was 6.6 ± 4.3 mm (range, 1.9 to 16.0 mm). Patients with other ocular diseases, a history of ocular surgery, ocular medication, or diabetes were excluded. Flare values in the tumor eyes were 1.18 ± 1.56 mg/ml (range, 0.36 to 5.82 mg/ml), whereas flare values in the clinically unaffected fellow eyes were 0.13 ± 0.06 mg/ml (range, 0.08 to 0.28 mg/ml) and in the healthy control eyes 0.13 ± 0.05 mg/ml (range, 0.07 to 0.25 mg/ml) (Figure). Differences between tumor eyes and both healthy control (Mann-Whitney test) and fellow eyes (*t*-test) were highly significant (P = .0001). No

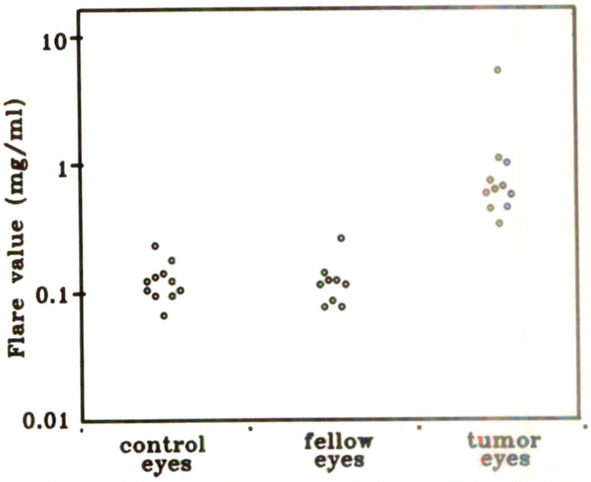

Figure (Küchle, Nguyen, and Naumann). Scatter plot of flare values in healthy control eyes (N = 11), healthy fellow eyes (N = 9), and eyes with choroidal melanomas (N = 11).

difference was found between fellow eyes and healthy control eyes (P = .82, Mann-Whitney test).

Slit-lamp assessment of normal or moderately increased aqueous flare is difficult and lacks objectivity, quantification, and reproducibility. In contrast, the laser flare-cell meter allows detection and quantification of even slightly increased flare values. The mechanisms by which aqueous flare is increased in eyes with choroidal malignant melanomas are obscure. Presumably, protein leaks through tumor vessels and impaired retinal pigment epithelium adjacent to the tumor into the vitreous from where it diffuses into the anterior chamber. Impairment of the blood-retina barrier and formation of serous subretinal exudate and shifting retinal detachment are well-known clinical and histopathologic features of uveal melanomas.[5] Tumor factors and toxic substances released by tumor cells, degenerating pigment epithelium, or altered photoreceptors may also play a role, although systemic effects on the anterior segment via the blood circulation are unlikely as fellow eyes showed no alteration of the blood-aqueous barrier.

Our findings suggest that the noninvasive laser flare-cell meter might be an effective tool for evaluating aqueous flare changes in eyes with intraocular tumors, and this instrument may also be helpful in the differential diagnosis of intraocular lesions.

References

1. Sawa, M., Tsurimaki, Y., Tsuru, T., and Shimizu, H.: New quantitative method to determine protein concentration and cell number in aqueous in vivo. Jpn. J. Ophthalmol. 32:132, 1988.
2. Oshika, T., Kato, S., Araie, M., and Masuda, K.: Aqueous flare intensity and age. Jpn. J. Ophthalmol. 33:237, 1989.
3. Ohara, K., Okubo, A., Miyazawa, A., and Sasaki, H.: Aqueous flare and cell meter in iridocyclitis. Am. J. Ophthalmol. 106:487, 1988.
4. Drews, R. C.: Management of postoperative inflammation. Dexamethasone versus flurbiprofen, a quantitative study using the new flare cell meter. Ophthalmic Surg. 21:560, 1990.
5. Zimmerman, L. E.: Malignant melanoma of the uveal tract. In Spencer, W. E. (ed.): Ophthalmic Pathology, vol. 3. Philadelphia, W. B. Saunders Company, 1986, pp. 2121–2125.

Hemoglobin SC Disease With Endogenous Endophthalmitis

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Individuals who are homozygous for sickle cell anemia (SS) are typically prone to septicemia by encapsulated bacteria secondary to splenic dysfunction from microinfarction. We treated a patient with hemoglobin SC disease, pneumococcal sepsis, pneumococcal meningitis, and bilateral endogenous endophthalmitis.

A 26-year-old black woman was seen at our institution because of severe frontal headaches without meningismus or photophobia. The patient had a temperature of 38.3 C, orthostatic hypotension, and a stiff neck. Results of laboratory tests included a white blood cell count of 21,700 mm^3 with 33% bands; a normal computed tomogram of the head; and a lumbar puncture with seven red blood cells, seven polymorphonuclear cells, and one monocyte per cubic millimeter of cerebrospinal fluid. Gram stain of the cerebrospinal fluid disclosed numerous gram-positive cocci in pairs, and was positive for pneumococcal antigen. Treatment with penicillin G, 2 million units intravenously every two hours, was begun.

On the night of admission an ophthalmology consultation was requested because of redness of the patient's right eye. Near-card visual acuity was R.E.: 20/200 and L.E.: 20/30. Bedside examination disclosed marked epithelial edema of the right cornea. Intraocular pressure was 32 mm Hg in the right eye and 17 mm Hg in the left eye by Schiötz tonometry. A presumptive diagnosis of angle-closure glaucoma was made, and treatment was begun with timolol 0.5% twice a day in the right eye and pilocarpine 2% four times a day in both eyes. The next day the patient remained confused but oriented to person, place, and time. Visual acuity was light perception with projection in the right eye and counting fingers at 10 feet in the left eye. The right pupil was 4 mm and the left was 3 mm with trace reactivity and no afferent pupillary defect. Tension was 46 mm Hg in the right eye and 18 mm Hg in the left eye. Angle structures of the right eye were not visible because of corneal edema but the angle of the left eye was open to scleral spur with occasional, small, peripheral anterior synechiae. The patient and her family refused both peripheral iridectomy and pupillary dilation. By two days after admission, the patient was disoriented to person, place, and time. Visual acuity was questionable light perception in the right eye and counting fingers at 3 feet in the left eye with applanation pressures of 27 mm Hg in the right eye and 13 mm Hg in the left eye. A 2-mm hypopyon was present in the right eye and there was no red reflex. Examination of the left fundus disclosed a miliary distribution of focal areas of retinitis. At this time vitreous and anterior chamber cultures of both eyes were obtained, and 1 mg of clindamycin and 0.3 mg of dexamethasone were injected intravitreally. Gram stains of the culture specimens showed no organisms, and cultures remained negative for three days. By four days after admission, areas of salmon-patch hemorrhage were seen bilaterally with areas of elevation extending into the vitreous with vitreous hemorrhage. On the basis of the clinical appearance, a hemoglobin electrophoresis was ordered, which disclosed hemoglobin SC disease. The patient remained hospitalized on a regimen of intravenous antibiotics. Her complicated hospital course included two intensive care unit stays with intubation for respiratory failure. At last examination, four months after admission, the patient's visual acuity was R.E.: 20/200 and L.E.: 20/20.

In a review of the eight cases of metastatic pneumococcal endophthalmitis described since the advent of antibiotics, Cheesbrough and associates[1] identified asplenia, cardiac valvular disease, and systemic lupus erythematosus as predisposing factors. Greenwald, Wohl, and Sell[2] also noted immune dysfunction as the etiologic predisposing factor. We believe ours is a unique case of endogenous endophthalmitis occurring secondary to sickle cell disease.

The failure to diagnose endogenous endophthalmitis promptly is not unusual. In the review of Greenwald, Wohl, and Sell,[2] 11 of 67 patients with endophthalmitis at first were thought to have conjunctivitis, acute glaucoma, or noninfectious uveitis. Our patient was receiving appropriate intravenous antibiotics, which makes it unlikely that delay in diagnosis adversely affected her. The finding that vitreous cultures were negative is not surprising inasmuch as she had previously received antibiotics intravenously. In cases where ocular cultures were positive, there has been a high correlation with positive cultures from other body sites.

We believe that hemoglobin SC disease should be considered a systemic disorder that can predispose an individual to endogenous endophthalmitis with encapsulated organisms. Presumably, this endophthalmitis is secondary to splenic dysfunction from microinfarction leading to difficulty with opsonization of encapsulated organisms.

References

1. Cheesbrough, J. S., Williams, C. L., Rustom, R., Bucknall, R. C., and Trimble, R. B.: Metastatic pneumococcal endophthalmitis. Report of two cases and review of literature. J. Infect. 20:231, 1990.
2. Greenwald, M. J., Wohl, L. G., and Sell, C. H.: Metastatic bacterial endophthalmitis. A contemporary reappraisal. Surv. Ophthalmol. 31:81, 1986.

Respiratory Arrest and New Retinal Hemorrhages After Retrobulbar Anesthesia

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Respiratory arrest is a rare complication of retrobulbar anesthesia.[1-4] Although the cause of this complication is in doubt, it is considered secondary to inadvertent injection of local anesthesia into the optic nerve sheath. The anesthesia then mixes with cerebrospinal fluid, diffuses through the subarachnoid space, and causes brainstem anesthesia including depression of the respiratory center.

Previous authors have reported this complication after using a 1.5-inch needle to perform a retrobulbar block.[2-4] They suggested that a shorter needle may avoid penetration of the optic nerve sheath. We encountered two cases

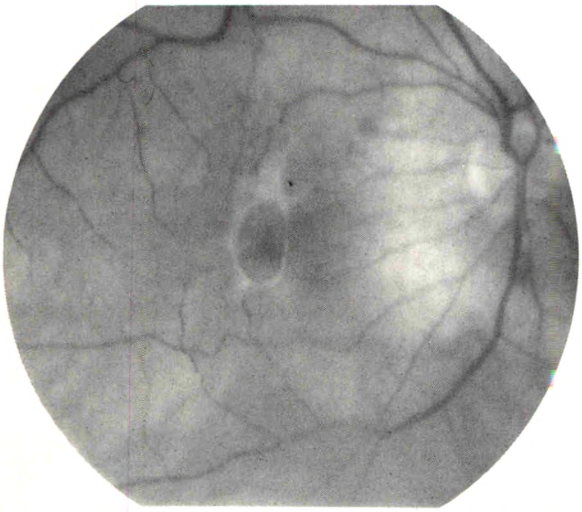

Fig. 1 (Cohen and associates). Case 1. Fundus photograph two months before accidental nerve sheath injection during retrobulbar block. Note the macular pucker and absence of retinal hemorrhages.

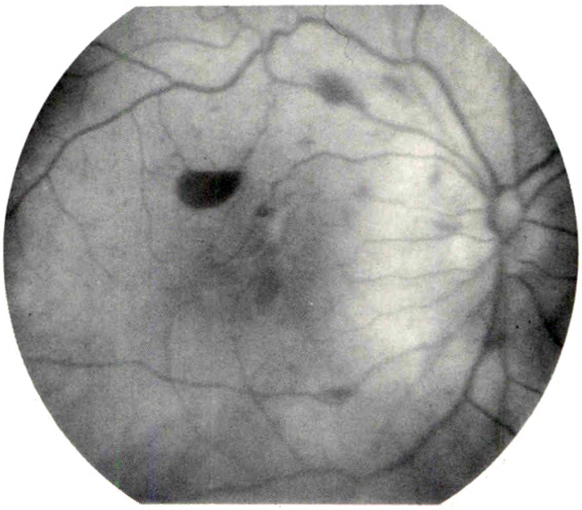

Fig. 2 (Cohen and associates). Fundus photograph of the same eye one day after accidental nerve sheath injection. Numerous preretinal and intraretinal hemorrhages are visible.

of respiratory arrest after retrobulbar injection with a 1.25-inch needle.

Case 1

On Aug. 6, 1990, a 44-year-old man with an epiretinal membrane was admitted to the outpatient ophthalmology service for repair of a macular pucker. On March 12, 1990, he had undergone scleral buckling for a retinal detachment that included the macula secondary to lattice degeneration in his right eye, which was performed under retrobulbar anesthesia administered through a 1.25-inch needle. The retina had been successfully reattached without complication. Subsequently, the patient noted visual deterioration, which was caused by an epiretinal membrane in his right eye. Figure 1 one shows the macular pucker.

Before retrobulbar injection, an anesthesiologist administered 1.5 mg of midazolam hydrochloride, 50 mg of fentanyl, and 100 mg of thiopental intravenously. Retrobulbar anesthesia was then administered by injection of 6 ml of a 50% mixture of 4% lidocaine and 0.75% bupivacaine with 150 units of hyaluronidase through a 1.25-inch, 25-gauge needle. During injection, the eye was positioned in primary gaze. Within two minutes, the patient awoke from the thiopental sleep, but complained of difficulty swallowing. He became somnolent, his blood pressure increased from 140/80 to 200/120 mm Hg, and his heart rate increased from 80 to 150 beats per minute. He stopped breathing and was promptly intubated by the anesthesiologist within five minutes of the retrobulbar injection.

The patient's contralateral pupil was fixed and dilated. Scattered preretinal and intraretinal hemorrhages were present in the right eye (Fig. 2). The patient was extubated 15 minutes later. Both of his eyes were akinetic, and he had no light perception. He remained stuporous for one hour. His ductions and visual acuity gradually returned to baseline within two hours. A full neurologic examination two hours after the event showed no residual abnormalities.

He subsequently underwent repair of his macular pucker one month later. Retrobulbar anesthesia of the same mixture was administered with a 1.25-inch needle without complication.

Case 2

On April 8, 1991, a 58-year-old man with a retinal detachment in his right eye was admitted for repair with a scleral buckle. The patient was sedated with the same agents described in Case 1. Retrobulbar anesthesia was administered by injecting 6 ml of a 50% mixture of 4% lidocaine and 0.75% bupivacaine with 150 units of hyaluronidase through a 1.25-inch, 25-gauge needle with the eye positioned in primary gaze.

Within two minutes, the patient's blood pressure increased from 110/80 to 220/110 mm Hg and his heart rate increased from 65 to 120 beats per minute. The patient's respiratory rate decreased. He was intubated and unresponsive for a period of 30 minutes. Upon awakening, the patient complained of decreased vision in both eyes and decreased hearing. The patient's ipsilateral and contralateral pupils were dilated. His fundus was unchanged.

The patient's cranial nerve deficits resolved within six hours. He underwent uncomplicated repair of his retinal detachment under general anesthesia the next evening.

The course in these patients is consistent with accidental injection into the subarachnoid space, causing brainstem anesthesia. There was evidence of multiple transient cranial nerve palsies distant from the site of injection. Depressed mental status and respiratory arrest are consistent with anesthesia of the brain stem, affecting the respiratory centers.

In Case 1, the anesthesiologist first feared accidental administration of medications that induced the respiratory arrest. The ophthalmic examination disclosed multiple cranial nerve palsies and retinal hemorrhages, which facilitated the diagnosis of brainstem anesthesia and enabled the anesthesiologist to treat this emergent complication properly.

The incidence of brainstem anesthesia after retrobulbar anesthesia is 0.09% to 0.8%.[1,3] When retrobulbar blocks are performed in an unmonitored setting, we recommend the use of an even shorter needle. In the office, we now perform all of our retrobulbar injections with a sharp, 25-gauge, 1.0-inch needle. This technique achieves excellent anesthesia and akinesia, while minimizing the risk of this serious complication.

References

1. Wittpen, J. R., Rapoza, P., Sternberg, P., Kuwashima, L., Saklad, J., and Patz, A.: Respiratory arrest following retrobulbar anesthesia. Ophthalmology 93:867, 1986.

2. Brookshire, G. L., Gleitsmann, K. Y., and Schenk, E. C.: Life-threatening complication of retrobulbar block. Ophthalmology 93:1476, 1986.

3. Ahn, J. C., and Stanley, J. A.: Subarachnoid injection as a complication of retrobulbar anesthesia. Am. J. Ophthalmol. 103:225, 1987.

4. Javitt, J. C., Addiegeo, R., Friedberg, H. L., Libonati, M. M., and Leahy, J. J.: Brain stem anesthesia after retrobulbar block. Ophthalmology 94:718, 1987.

Corneal Endothelial Dysfunction in Digoxin Toxicity

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Ocular manifestations of digoxin toxicity include blurred vision, xanthopsia, scotomas, and photopsia.[1] Various sites of toxicity within the central nervous system and the eye have been implicated. Electroretinographic studies have shown direct retinal toxicity.[2] Smith and Michtavage[3] described the ocular effects of topically administered cardiac glycosides, which included a slight lowering of intraocular pressure but, in addition, a specific keratopathy, characterized by corneal stromal edema and folds in Descemet's membrane. We recently observed a patient with systemic digoxin toxicity and documented corneal edema that resolved after digoxin levels returned to normal.

A 60-year-old woman was seen on Aug. 24, 1990, because of a five-day history of blurred vision, greater in the right eye than in the left eye, in association with nausea and vomiting. She complained of a gray-yellow coloring of

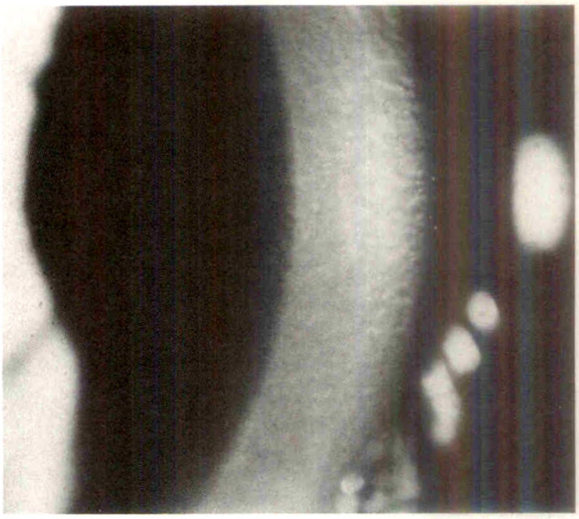

Fig. 1 (Madreperla, Johnson, and O'Brien). Slit-lamp photograph of cornea in the right eye on Aug. 24, 1990. Corneal thickening and mild folds in Descemet's membrane are present.

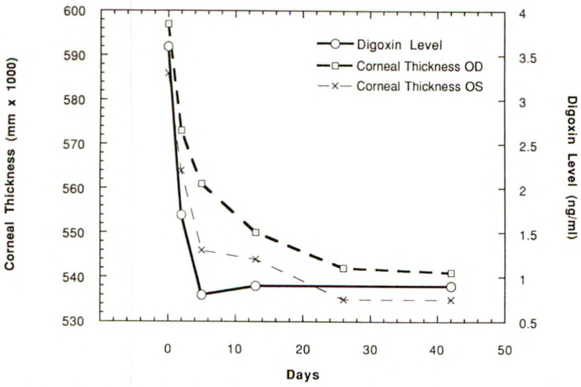

Fig. 2 (Madreperla, Johnson, and O'Brien). Corneal thickness and digoxin level as a function of days after Aug. 24, 1990. There was a gradual decrease in corneal thickness in both eyes after the return of digoxin to therapeutic levels (0.8–2.0 ng/ml). OD indicates right eye; OS, left eye.

objects, photopsia, and subjectively worse vision outdoors in bright light. Systemic medications included furosemide, warfarin sodium, phenytoin, and digoxin (recently increased to 0.2 mg, four times a day).

Best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/50. The pupil was normal. Slit-lamp biomicroscopy disclosed moderate corneal stromal edema in both eyes with folds in Descemet's membrane in the right eye (Fig. 1). Only mild cornea guttata was present. The anterior chambers were well formed and clear, and irides were postsurgical. Well centered intraocular lenses were present in the posterior chamber. The right eye had mild posterior capsular opacification. The fundi appeared normal ophthalmoscopically. The patient correctly identified two of 12 Ishihara color plates with the right eye and one of 12 with the left eye. Central corneal thickness by ultrasonic pachymetry was 0.599 mm in the right eye and 0.586 mm in the left eye (Fig. 2). The serum digoxin level was increased to 3.6 ng/ml. Digoxin was discontinued until the serum level reached 1.0 ng/ml at which time digoxin was restarted at 0.2 mg per day. In both eyes exponential declines in central corneal thickness were observed (time constants, R.E.: 4.44 days; L.E.: 3.24 days; Fig. 2). Serum digoxin level declined exponentially with a time constant of 1.60 days. Visual acuity eventually returned to 20/25 in each eye.

Resolution of the patient's corneal edema occurred as digoxin toxicity resolved. Interestingly, serum levels of digoxin were normal within days but corneal edema resolved more slowly.

Maurice[4] proposed the location of a fluid pump in the cornea to explain the transfer of fluid from the stroma to the aqueous humor by means of an energy-consuming mechanism residing in the corneal endothelium. Actually, the driving force for dehydration probably involves energy-dependent ion transport. The endothelium is enriched in sodium-potassium adenosine triphosphatase, an ion pump that is probably responsible for corneal deturgescence. This enzyme is inhibited by digoxin and other cardiac glycosides such as ouabain. We propose that the high serum concentration of digoxin in our patient resulted in aqueous humor concentrations sufficient to inhibit corneal endothelial sodium-potassium adenosine triphosphatase, thereby causing corneal edema. Patients with compromised endothelium may be at greater risk for corneal edema during digoxin toxicity. Our patient was pseudophakic and had mild cornea guttata.

References

1. Withering, W.: An Account of Fox Glove and Some of Its Medical Uses. With Practical Remarks on Dropsy and Other Diseases. Birmingham, England, M. Swinney, 1785, p. 184.

2. Weleber, R. G., and Shults, W. T.: Digoxin retinal toxicity. Clinical and electrophysiological evaluation of a cone dysfunction syndrome. Arch. Ophthalmol. 99:1568, 1981.

3. Smith, J. L., and Michtavage, R. C.: The ocular effects of topical digitalis. Am. J. Ophthalmol. 56:889, 1963.

4. Maurice, D. M.: The location of the fluid pump in the cornea. J. Physiol. 221:43, 1972.

Delayed Trifluridine Treatment of Subepithelial Corneal Infiltrates

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Subepithelial corneal infiltrates frequently develop in the course of epidemic adenoviral keratoconjunctivitis, but similar subepithelial infiltrates can be seen in nummular keratitis Dimmer, in herpes zoster and varicella keratitis, and even in some cases of herpes simplex.[1] Reduced visual acuity or reduced contrast sensitivity with central localization of the infiltrates, prolonged photophobia, and conjunctivitis sicca may be the long-term sequelae that require prolonged symptomatic lubricating therapy. In many cases, topical corticosteroid therapy results in complete resolution of the infiltrates, sometimes with their re-appearance after tapering of the corticosteroid dosage. In some patients the infiltrates persist for years despite corticosteroids.

A 14-year-old boy was first seen in 1986 for the correction of myopia. Multiple, bilateral, subepithelial corneal infiltrates were considered to be residue of an earlier epidemic keratoconjunctivitis. In 1989, the patient was seen because of photophobia and conjunctivitis sicca. He was treated topically with fluorometholone and polyvinyl alcohol eyedrops. The infiltrates did not resolve with corticosteroids, but the patient temporarily had no symptoms. In April 1991, he was seen again. He recalled having had chickenpox in 1985, a few months before the diagnosis of the corneal infiltrates. The corneal infiltrates now appeared to be partly subepithelial, partly epithelial, resembling the necrotic plaque epitheliopathy rarely seen in herpes simplex keratitis but with smooth corneal surfaces. The corneal sensitivity was not decreased. Topical therapy with trifluridine eyedrops and trifluridine ointment was begun. Within ten days the corneal infiltrates disappeared in both eyes but slight filiform keratitis developed in the right eye. Trifluridine eyedrops were stopped and epithelization therapy was continued. No corticosteroids were used. Four weeks later a few subepithelial opacities reappeared and were treated with both trifluridine and lubricants. Further therapy with lubricants and low-dosage fluorometholone resulted in clear corneas.

Encouraged by this finding I used trifluridine in five patients with corneal subepithelial infiltrates, which had persisted about one year after epidemic keratoconjunctivis, and one patient with corneal infiltrates that had persisted for almost six years. In all patients, previous topical corticosteroid therapy failed to resolve the infiltrates. Within one week of the trifluridine treatment, some of the subepithelial infiltrates disappeared and the degree of opacity of the remaining infiltrates decreased markedly. Initially, some infiltrates increased in size somewhat during the therapy but were almost invisible after four weeks of topical trifluridine therapy (Figure). In two patients (including the patient with a six-year history of corneal infiltrates), visual acuity increased three Snellen lines after treatment. In two patients, visual acuity was one line better, and in one it remained the same.

An early report on topical trifluridine therapy in acute adenovirus type 3 infection indicated no apparent effect on the course of the infection.[2] The effect on the corneal involvement, which is rare with adenovirus type 3 could not be studied in this experimental setting. Trifluridine was found to be effective in inhibiting the replication of adenoviruses types 8, 13, and 19 in vitro[3] but since then no systematic study has been undertaken on the possible inhibitory effect of trifluridine on the formation of subepithelial corneal infiltrates during adenoviral keratoconjunctivitis. In one study the severity of

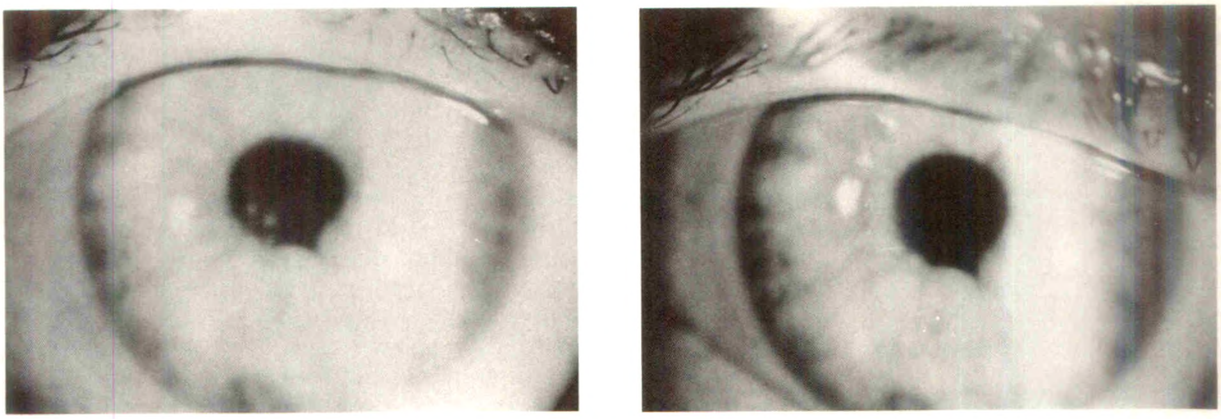

Figure (Kana). Left, Subepithelial corneal infiltrates after epidemic keratoconjunctivitis before trifluridine therapy. Right, The same eye after seven days of topical trifluridine therapy.

epidemic keratoconjunctivitis caused by type 19 adenovirus was decreased through topical trifluridine therapy, which was not the case with several other serotypes.[4]

The mechanism of this delayed trifluridine effect is obscure, because we cannot be sure of the infective agent involved. Proof of possible persistence of a viral antigen in the infiltrates has not been demonstrated. It seems unlikely that the trifluridine is cytotoxic to lymphocytes, fibroblasts, or both that are known to be present immediately beneath Bowman's membrane[5] in the infiltrates. Previous corticosteroid therapy did not alter the corneal infiltrates appreciably in these patients. Additional observations and laboratory studies are needed to understand the effect of trifluridine on the opacities.

References

1. Vastine, D. W., and Wilner, B. I.: Adenoviridae. In Darell, R. W. (ed.): Viral Diseases of the Eye. Philadelphia, Lea & Febiger, 1985, pp. 131–146.
2. Little, J. M., Lorenzetti, D. W. C., Brown, D. C., Schweem, H. H., Jones, B. R., and Kaufman, H. E.: Studies of adenovirus type III infection treated with methisazone and trifluorothymidine. Proc. Soc. Exp. Biol. Med. 127:1028, 1968.
3. Lenette, D. A., and Eiferman, R. A.: Inhibition of adenovirus replication in vitro by trifluridine. Arch. Ophthalmol. 96:1662, 1978.
4. Darougar, S., Quinlan, M. P., Gibson, J. A., and Jones, B. R.: Epidemic keratoconjunctivitis and chronic papillary conjunctivitis in London due to adenovirus type 19. Br. J. Ophthalmol. 61:76, 1977.
5. Lund, O. E., and Stefani, F. H.: Corneal histology after epidemic keratoconjunctivitis. Arch. Ophthalmol. 96:2085, 1978.

A Simplified Method for Demonstration and Isolation of *Acanthamoeba* Organisms From Corneal Scrapings and Lens Care Systems

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Free-living amebae of the genus *Acanthamoeba* have become clinically important as infectious agents of the human cornea[1] and of the central nervous system.[2] In the cornea, chronic destructive keratitis is common while a granulomatous amebic encephalitis occurs when the central nervous system is invaded. Diagnosis may be made by demonstrating amebae in corneal scrapings or biopsy specimens,[3] by direct agar cocultivation of amebae with *Escherichia coli*,[4] or after enrichment and filtration of specimens placed in ameba saline-transport medium.[5]

We recently diagnosed *Acanthamoeba* keratitis in a patient in whom the causative ameba was identified in Giemsa-stained smears of corneal scrapings and by the observation of numerous amebae (trophozoites) and cysts by phase-contrast microscopy of the fluid from the contact-lens case. To document the *Acanthamoeba* keratitis further, corneal scrapings were inoculated to nutrient agar seeded with *E. coli*. After 21 days of observation, cultures were negative for amebae. Concomitantly, the contact-lens bathing solution was inoculated to bacteriologic media. *Xanthamonas maltophilia* and *Serratia plymuthica* were isolated, whereas the culture of conjunctival scrapings was bacteriologically sterile.

Because of the presence of *Acanthamoeba* trophozoites and cysts in the contact-lens solution, we postulated that the *X. maltophilia* or *S. plymuthica*, or both, served as bacterial substrates for the growth of the *Acanthamoeba* organisms. To test this hypothesis, 0.1 ml of the contact-lens solution was inoculated to four tubes (12 × 75 mm), each containing 2.5 ml of sterile physiologic saline to which 0.5 ml of a turbid suspension of the two bacterial species was added. The tubes were incubated at 37 C, and at daily intervals a drop was removed from the sedimented layer and examined by phase-contrast microscopy for the presence of, and increased number of, amebic trophozoites and cysts. Within 48 hours, cocultivation in this manner led to a marked increase in the number of actively motile amebic trophozoites interspersed with clearly definable cysts (Figure). The cultures have now been maintained for over four months with weekly passage of 0.5 ml of *Acanthamoeba* suspension as described. *Acanthamoeba* organisms achieve a concentration of approximately 2×10^5/ml with approximate-

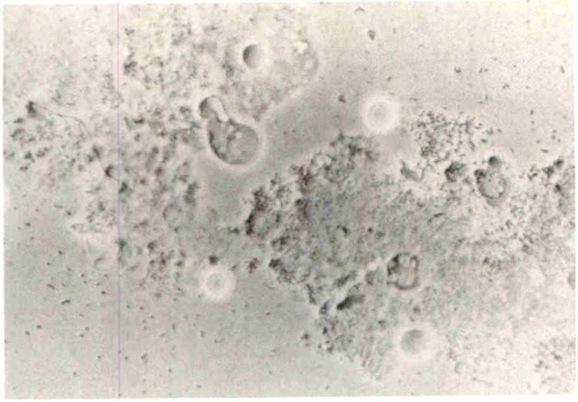

Figure (Bottone, Qureshi, and Asbell). Trophozoite and cysts of *Acanthamoeba* amplified in normal saline containing *X. maltophilia* and *S. plymuthica* as seen by phase-contrast microscopy (× 800).

ly 30% trophozoites as determined by hemocytometer count.

Because this amplification technique was easy to perform, we recommend that cocultivation with *E. coli* (or other suitable bacterial substrate) in a saline suspension be used for clinical (corneal) specimens as well, and for fluid derived from the lens-care system. This technique obviates the low power (× 10) scanning of an agar surface in search of amebic trophozoites, or the transfer of agar blocks containing amebae to new seed plates precoated with bacteria.[4] Further, in a liquid milieu, trophozoite movement is more easily discerned as contrasted to the more restricted amebic motility imposed by an agar matrix.

References

1. Visvesvara, G. S., and Stehr-Green, J. K.: Epidemiology of free-living *Ameba* infections. J. Protozool. 37:255, 1990.
2. Martinez, A. J.: Free-living amoebas. Pathogenic aspects. A review. Protozo. Abstr. 7:293, 1983.
3. Johns, K. J., Head, W. S., Elliot, J. H., and O'Day, D. M.: Isolation and identification of *Acanthamoeba* in corneal tissue. CLAO J. 13:272, 1987.
4. Visvesvara, G. S.: Free-living pathogenic amoebae. In Lennette, E. H., Balows, A., Hausler, W. J., and Truant, J. P. (eds.): Manual of Clinical Microbiology, ed. 3. Washington, D.C., American Society for Microbiology, 1980, pp. 704–708.
5. Gradus, M. S., Keenig, S., B., Hyundiuk, R. A., and DeCarlo, J.: Filter-culture technique using amoeba saline transport medium for the noninvasive diagnosis of *Acanthamoeba* keratitis. Am. J. Clin. Pathol. 92:682, 1980.

Congenital Lacrimal Fistula Associated With Down's Syndrome

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Michael P. Clarke, F.C.Ophth.,
Sheila Brazel, M.D.,
J. Donald Morin, F.R.C.S.(C.),
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Congenital lacrimal fistulas are rare developmental anomalies of the nasolacrimal drainage apparatus. Birchansky and associates[1] stated that usually there are no associated congenital systemic anomalies. We encountered congenital lacrimal fistulas in five patients with karyotypic trisomy 21 (Down's syndrome). External ocular findings in Down's syndrome include epicanthus, mongoloid slanting of the palpebral fissures, blepharitis, entropion, trichiasis, and congenital shortening of eyelid skin, which results in ectropion.[2,3] Coincidental congenital blockage of the nasolacrimal duct in a patient with Down's syndrome has also been described.[4]

Case 1

A 4-year-old girl with Down's syndrome had a history of epiphora and blepharitis since birth. She had bilateral blepharitis, but there was no right upper punctum. A fistula communicating directly with the nasolacrimal sac opened onto the skin 3 mm medial to the right medial canthus. It was excised to relieve the epiphora.

Case 2

A 4-year-old boy with Down's syndrome was examined for epiphora in the left eye since birth while he was an inpatient for surgical repair of a ventriculoseptal defect. He underwent excision of the fistula, and symptoms were relieved.

Case 3

A routine ophthalmic examination of a 2-month-old boy with Down's syndrome showed an asymptomatic left lacrimal fistula opening onto the skin below the inferior punctum. During eight months of follow-up, the fistula has remained asymptomatic, and no treatment was offered.

Case 4

Parents of a 2-week-old boy with Down's syndrome noticed a skin opening inferomedial to the lower punctum. This was confirmed as a lacrimal fistula during ophthalmic examination. The fistula has remained asymptomatic during seven months of follow-up, and no treatment was offered.

Case 5

A 7-month-old girl with Down's syndrome had a history of blepharitis and epiphora since birth. Ophthalmic examination disclosed that in addition to bilateral blepharitis she had a lacrimal sac fistula opening onto the skin inferomedial to the left lower punctum. The fistula was excised when the child was 11 months old. After 34 months of follow-up there has been no recurrence of epiphora although she still suffers from blepharitis.

In patients who have Down's syndrome and blepharitis and epiphora, we recommend that a thorough search be undertaken for associated congenital lacrimal fistulas. We believe these five cases represent more than coincidence. Congenital lacrimal fistulas should be considered as one of the ophthalmologic associations of Down's syndrome. Treatment consists of observation, but if symptoms cannot be tolerated, the fistula should be excised, with or without concurrent dacryocystorhinostomy.[1,5]

References

1. Birchansky, L. D., Nerad, J. A., Kersten, R. C., and Kulwin, D. R.: Management of congenital lacrimal sac fistula. Arch. Ophthalmol. 108:388, 1990.
2. Catalano, R. A.: Down syndrome. Surv. Ophthalmol. 34:385, 1990.
3. Morris, R. J., and Collin, J. R. O.: Functional lid surgery in Down's syndrome. Br. J. Ophthalmol. 73:494, 1989.
4. Awan, K. J.: Uncommon ocular changes in Down's syndrome (mongolism). J. Pediatr. Ophthalmol. Strabismus 14:215, 1977.
5. Welham, R. A. N., and Bergin, D. J.: Congenital lacrimal fistulas. Arch. Ophthalmol. 103:545, 1985.

Primary Eyelid Non-Hodgkin's Lymphoma in a Patient With Acquired Immunodeficiency Syndrome

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Andrew G. Fieo, M.S.,
and Dean E. Wolz, M.D.

Department of Ophthalmology, Penn State University College of Medicine (S.H.G., A.G.F.), and Department of Medicine, York Hospital (D.E.W.). Supported in part by patients and contributors of the Department of Ophthalmology, Penn State University College of Medicine, Hershey, Pennsylvania; Research to Prevent Blindness, Inc., New York, New York; and Pennsylvania Lions Vision and Research Center, Hershey, Pennsylvania.

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Recurrent opportunistic infections and unusual neoplasms are characteristic of acquired immunodeficiency syndrome (AIDS). Ocular manifestations of human immunodeficiency virus (HIV) infection include retinal microangiopathy, cytomegalovirus retinitis, eyelid and conjunctival Kaposi's sarcoma, and neuro-ophthalmic disorders.[1] Primary periocular neoplasms, other than Kaposi's sarcoma, have been reported infrequently in patients with AIDS. We encountered a case of large-cell, non-Hodgkin's lymphoma of the eyelid in a woman with HIV infection. This is a unique case of primary eyelid lymphoma in an HIV-infected patient.

A 34-year-old woman was referred to one of us (S.H.G.) because of a three-week history of progressive swelling of the right lower eyelid. Medical history disclosed HIV infection, believed to have been contracted from a blood transfusion for anemia five years previously, and pancytopenia. The right lower eyelid was erythematous, tender, and diffusely thickened to 1 cm (Figure). A biopsy specimen disclosed large-cell, non-Hodgkin's lymphoma (B-cell type). The occurrence of lymphoma in an HIV-infected patient established the diagnosis of AIDS.

Three days after the biopsy, the patient was hospitalized for disseminated herpes zoster. Computed tomography of the abdomen and chest failed to demonstrate disseminated lymphoma. Treatment consisted of radiation therapy to the right lower eyelid (4,000 cGy). Systemic chemotherapy was not attempted because of the patient's myelosuppressed state. The

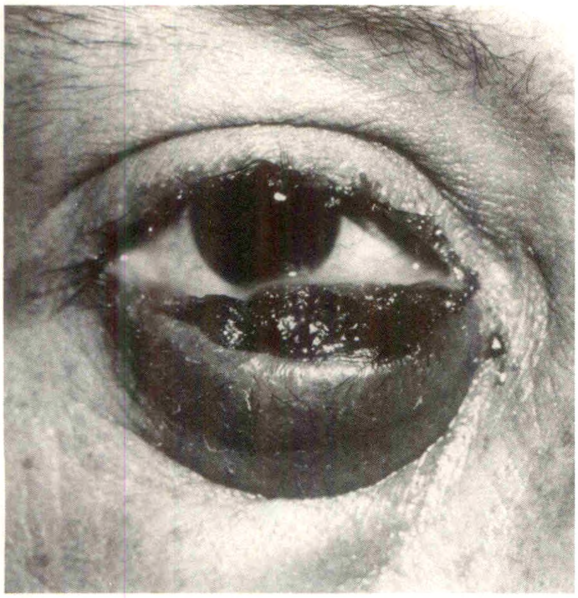

Figure (Goldberg, Fieo, and Wolz). External appearance of markedly thickened, edematous, and erythematous right lower eyelid.

nodule on the right lower eyelid regressed rapidly. Eighteen months after treatment, there was no evidence of right, lower eyelid or disseminated lymphoma.

Orbital lymphoma as a manifestation of AIDS has been reported infrequently. One autopsy case was identified in a series of 200 AIDS patients.[1] A 28-year-old AIDS patient who had "Burkitt's-like" lymphoma involving the orbit and spine was described in 1982.[2] Antle and associates[3] documented a case of non-Hodgkin's lymphoma in the orbit of a 25-year-old man with AIDS. That patient had hepatosplenomegaly and enlargement of retrocrural and retroperitoneal lymph nodes. Right medial orbit and ethmoid sinus lymphoma was the primary manifestation of AIDS in a 33-year-old man with proptosis.[4]

Non-Hodgkin's lymphoma of the orbit is uncommon.[3] These tumors generally occur in the fifth to seventh decade, are usually unilateral, tend to be located in the anterior orbit, and have no external inflammatory features. Non-Hodgkin's lymphoma in the population positive for HIV is significantly more prevalent than in the general population and may occur in the third decade. The typical clinical manifestation is that of a rapidly enlarging nodal or extranodal mass with the histologic pattern of large-cell lymphoma. Treatment consists of radiation and chemotherapy. The association of non-Hodgkin's lymphoma and AIDS was recognized by Zeigler and associates[5] in 1984, who suggested non-Hodgkin's lymphoma as a criterion for diagnosis of AIDS, and noted the poor prognosis associated with non-Hodgkin's lymphoma in AIDS patients.

Our patient's eyelid lymphoma, without evidence of systemic disease at the time of diagnosis and continuing disease-free status 18 months after radiation therapy alone, is unusual.

References

1. Jabs, D. A., Green, W. R., Fox, R., Polk, B. F., and Bartlett, J. G.: Ocular manifestations of acquired immune deficiency syndrome. Ophthalmology 96:1092, 1989.

2. Zeigler, J. L., Miner, R. C., Rosenbaum, E., Lennette, E. T., Shilliote, E., Casavant, C., Drew, W. L., Mintz, L., Gershow, J., Greenspan, J., Beckstead, J., and Yamamoto, K.: Outbreak of Burkitt's-like lymphoma in homosexual men. Lancet 2:631, 1982.

3. Antle, C. M., White, V. A., Horsman, D. E., and Rootman, J.: Large cell orbital lymphoma in a patient with acquired immune deficiency syndrome. Ophthalmology 97:1494, 1990.

4. Mansour, A. M.: Orbital findings in acquired immunodeficiency syndrome. Am. J. Ophthalmol. 110:706, 1990.

5. Zeigler, J. L., Beckstead, J. A., Volberding, P. A., Abrams, D. I., Levine, A. M., Lukes, R. J., Gill, P. S., Burkes, R. L., Meyer, P. R., Metroka, C. E., Mouradian, J., Moore, A., Riggs, S. A., Butler, J. J., Cabanillas, R. C., Hersh, E., Newell, G. R., Laubenstein, L. J., Knowles, D., Odajnyk, C., Raphael, B., Koziner, B., Urmacher, C., and Clarkson, B. D.: Non-Hodgkin's lymphoma in 90 homosexual men. Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. N. Engl. J. Med. 311:565, 1984.

Defining Mean Visual Acuity

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Vila-Coro and Vila-Coro[1] and Holladay and Prager[2] have suggested ways of calculating "mean" visual acuity. Statisticians reserve the word "mean" to denote the average of a set of numbers and collectively refer to means, medians, geometric means, and so forth, which somehow represent typical values in a population, as location parameters or measures of central tendency.[3] I wish to raise the issue that the appropriate measure of central tendency to utilize with Snellen fractions depends on the context of specific application. For example, consider the placement of a traffic sign to be seen by a certain population of drivers with varying visual acuities. One may ask two questions: (1) What is the average distance at which the drivers see the sign? (2) What is the average size (visual angle) the drivers need to see the sign at a specified distance? For simplicity, assume that a driver with visual acuity of 20/20 can read it at one mile away, then a driver with visual acuity of 20/60 should see it at one third of a mile, and so forth. The answer to question 1 is to follow the suggestion of Vila-Coro and Vila-Coro[1] of converting the Snellen fractions to decimals, averaging them, then expressing the result as a fraction with the numerator 20. If there are only two drivers with visual acuities of 20/20 and 20/60, the calculation is $(20/20 + 20/60)/2 = (1.00 + 0.33)/2 = 0.67 = 20/30$, and the answer to question 1 is 20/30 mile. To answer 2, the visual angles are proportional to the denominators of Snellen fractions, so the average is $(20 + 60)/2 = 40$, corresponding to the visual acuity 20/40. The quantity 20/40 obtained in this way is called the harmonic mean of 20/20 and 20/60.

The first question requires the average of Snellen fractions and the second needs the harmonic mean. Although the previous example is deliberately trivial to keep the calculations as brief as possible, it illustrates that either measure of central tendency applies in the proper context. The use of the harmonic mean is neither a contrivance nor an isolated oddity in medicine. It is used, for example, in calculating the mean creatinine clearance in renal physiology because the clearance depends inversely on plasma creatinine levels. One properly uses the harmonic mean, P, of plasma creatinine levels in the formula $C = UV/P$ to obtain the mean creatinine clearance.

Holladay and Prager[2] advocate using the geometric mean as a measure of central tendency of visual acuities, calculated as the antilogarithm of the average of the logarithms of the visual acuities. This quantity is always less than the mean (average) and greater than the harmonic mean (unless all visual acuities are equal), so they state that it neither overestimates nor underestimates mean visual acuity. The geometric mean works well to give average spatial positions of letter lines on modern visual acuity charts with letter sizes following a geometric progression, but so will the harmonic mean on charts on which the letter sizes follow an arithmetic progression as on older Snellen charts. Different measures of central tendency match up well with certain schemes of letter-size spacing.

Statistical quantities are used to summarize data, but, more importantly, for testing experimental hypotheses and estimating parameters of population distributions. Although using the average or the geometric mean consistently may be acceptable to describe one's samples, the question of which to use for hypothesis testing is a far weightier matter because the choice of one over the other may reverse the conclusion of one's work. A solution is to use nonparametric methods whenever possible. These use statistics such as the median, which are easy to compute, but which do not require assumptions about the distribution of the populations from which the sample is taken. Distributions of samples of visual acuities tend to be skewed, so means and standard deviations omit information, which is a reason nonparametric descriptive statistics such as medians, quartiles, and deciles can provide a more detailed summary of a sample.

References

1. Vila-Coro, A. A., and Vila-Coro, An. A.: Mean visual acuity. Am. J. Ophthalmol. 107:564, 1989.

2. Holladay, J. T., and Prager, T. C.: Mean visual acuity. Am. J. Ophthalmol. 111:372, 1991.

3. Naiman, A., Rosenfeld, R., and Zirkel, G.: Understanding Statistics. New York, McGraw-Hill, 1977, p. 9.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

The Laser Step in Early Glaucoma

EDITOR:

We read with interest the Perspective, "The laser step in early glaucoma therapy," by E. M. Van Buskirk (Am. J. Ophthalmol. 112:87, July 1991). Dr. Van Buskirk discusses the results of the Glaucoma Laser Trial[1] and provides his observations concerning the study. We wish to comment on those observations.

Dr. Van Buskirk is correct, as we have also noted, that the two Glaucoma Laser Trial treatment regimens are different in that one eye is treated initially with argon laser trabeculoplasty and the other eye is treated initially with medicine. He proceeds to specify the subsequent therapeutic steps and dwells on the inappropriateness of number of steps as an index for comparing the two treatment regimens.

Dr. Van Buskirk's preoccupation with number of steps as an outcome measure is surprising and unfortunate. That preoccupation is at odds with our treatment of the data. We did not use number of steps as a primary outcome measure. The steps constituted the protocol for medical treatment, and our discussion of number of steps was limited to the reasons for stepping.

In dwelling on the number of steps, Dr. Van Buskirk makes the same mistake as Dr. Lichter made in his editorial[2] concerning the Glaucoma Laser Trial results. Dr. Van Buskirk states: ". . . Ominous was the suggestion that visual field deterioration accounted for nearly twice as many medication step changes in the laser-treated as the nonlaser-treated eyes." No. Visual field changes accounted for proportionately twice as many medication step changes for laser-treated eyes as for nonlaser-treated eyes. However, as we stated in our publication, there were twice as many steps for the medication first eyes as for the laser first eyes, and the actual number of steps caused by visual field deterioration was 50 for the laser-treated eyes vs 57 for the nonlaser-treated group.

This emphasis on number of steps also obscures important findings of the trial that relate to time to prescription changes and intraocular pressure differences between the two treatment regimens. The existence of, on average, a 2-mm Hg lower pressure for eyes started on laser treatment as compared to eyes started on medicine is ignored, a curious oversight in view of the presumed role of increased pressure in causing glaucomatous damage.

In his Perspective, Dr. Van Buskirk states: "The Glaucoma Laser Trial has shown conclusively that initial laser treatment offers no real advantage to medical therapy for the patient with newly diagnosed glaucoma, except a couple of years' grace before starting other medications." The statement represents a giant leap into the unknown in that it depends on a crystal ball with which one predicts the future course of a chronic condition and the most appropriate treatment for that condition on the basis of data presented for a mere two years of follow-up. He ignores the fact that the laser-treated eyes fared better than their medically treated counterparts throughout with regard to intraocular pressure. Further, he dismisses as trivial the fact that the use of medicine is delayed without any appreciation for what that delay may mean in the short or long term. To trivialize that difference one has to assume medicines are uniformly safe and without side effects. There are plenty of data to the contrary.

Dr. Van Buskirk states that the Glaucoma Laser Trial ". . . suggests initial laser treatment to be disadvantageous compared to laser treatment placed toward the end of the medical sequence of therapy." His support for the statement involves comparison of five-year success rates derived from observational studies involving maximal medical treatment before proceeding to laser treatment[3,4] with rates derived from the trial after two years of treatment. In doing so, he blithely ignores the fact that the rates cited are not comparable; the former come from observational studies of largely unselected patients and the latter from a randomized trial of selected patients whose eyes were randomly assigned to treatment.

Dr. Van Buskirk states that the Glaucoma Laser Trial Research Group concluded that the ". . . study encouraged the application of laser trabeculoplasty as initial therapy by postponing the onset of medical therapy with its attendant inconvenience and risk of drug side effects." Actually, the statement of the Research Group was ". . . limitations and caveats nothwithstanding, results of the [Glaucoma Laser Trial] are encouraging regarding the usefulness of [argon laser trabeculoplasty] as an initial treatment for [primary open-angle glaucoma]." We did not encourage its use. We stated that the results were encouraging regarding its use.

All trials, including ours, represent approximations to reality and involve compromises and limitations. However, it is not that trials are imperfect which reviewers and readers should focus on, but rather, whether those imperfections are serious enough to cause one to doubt the results and conclusions of the trial. Rather than attempting to talk these results under the table, our energies should go to doing other trials to provide assessments of the therapy used for treatment of glaucoma, including the current standard—medicines. We would rather take small steps for mankind in that way than giant steps backward by forcing results of trials to conform to the prevailing impressions concerning the merits of medical treatment.

HUGH BECKMAN, M.D.
Glaucoma Laser Trial Chairman
CURTIS L. MEINERT, Ph.D.
Coordinating Center Director

References

1. The Glaucoma Laser Trial Research Group: The Glaucoma Laser Trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines. Ophthalmology 97:1403, 1990.
2. Lichter, P. R.: Practice implications of the Glaucoma Laser Trial. Ophthalmology 97:1401, 1990.
3. Grinich, N. P., Van Buskirk, E. M., and Samples, J. R.: Three year efficacy of argon laser trabeculoplasty. Ophthalmology 94:858, 1987.
4. Schwartz, A. L., Love, D. C., and Schwartz, M. A.: Long-term followup of argon laser trabeculoplasty for uncontrolled open-angle glaucoma. Arch. Ophthalmol. 103:1482, 1985.

Reply

EDITOR:

I appreciate the interest of Drs. Beckman and Meinert in my Perspective article. I will not reiterate my previous discussion. I would like to address some specific and relevant areas of misunderstanding.

Drs. Beckman and Meinert criticize my "preoccupation" with the number of treatment step changes as an outcome, believing I should have focused on the intraocular pressure. The clinician might legitimately ask whether or not slightly more hypotensive potency is critical for selecting a first line of therapy. I submit that one does not always select the most potent agent for initial treatment, saving it for a subsequent, more critical time, in the disease course. Because of the study design, it should come as no surprise that the intraocular pressure values were lower in the laser-first eyes. They were always at least one therapeutic step ahead of the medicine-first eyes. All laser-first eyes had had laser at least, or laser plus timolol. None of the medicine-first eyes had received laser, and many had had timolol withdrawn. Perhaps confusion about the hypothesis that was being investigated by this study has compromised our ability to interpret the results.

My conclusion that a two-year delay in medical treatment is relatively meaningless does not "trivialize" the issue of drug side effects. I am familiar with the side effects of medical therapy. If the Glaucoma Laser Trial shows anything, it demonstrates that the issue is not whether or not the laser patients are exposed to medical therapy. Despite initial laser therapy, 56% required drug therapy within two years. The issue becomes whether or not a mere two-year delay of medical therapy at the dawn of a lifelong battle with glaucoma assumes any real clinical significance.

Neither the Glaucoma Laser Trial authors nor I doubt the existence of imperfections in their study. As Drs. Beckman and Meinert rightly point out, we differ in our assessment of how seriously those imperfections impact interpretation of the results. I feel that the incomparability of the two study groups makes meaningful scientific or clinical conclusions difficult. They believe their study provides useful information. Before we citizens invest in any further studies we must identify the hypothesis to be tested, examine its validity, determine its clinical relevance, and consider the potential societal benefit to be derived from its resolution.

A final major issue lies with the authors' own interpretation of their study. Drs. Beckman and Meinert deny they have encouraged the use of laser as initial therapy, but only stated their results were encouraging. Semantic subtlety aside, in the March 1, 1991, issue, Ocular Surgery News quoted Dr. Beckman: "Certainly the trial has shown, over a two-year period, that there is no reason we can tell not to treat [initially] with the laser." If this quote is inaccurate or does not reflect the conclusions of the authors of the study, the time is ripe for clarification. We ophthalmologists are confused.

I appreciate the opportunity to continue dialogue on this important and interesting issue.

E. MICHAEL VAN BUSKIRK, M.D.
Portland, Oregon

Human Immunodeficiency Virus Disease Epidemiology and Nosocomial Infection

EDITOR:

In the article, "Human immunodeficiency virus disease epidemiology and nosocomial infection," by R. Ortiz and T. M. Aaberg (Am. J. Ophthalmol. 112:335, September 1991), the lucid discussion on seroconversion, risk of HIV infection in surgeons, and adherence to universal precautions brought to mind several practical considerations that we have invoked at the University of Florida during retinal reattachment surgery.

With known HIV-positive patients we have adopted several measures to reduce exposure of all operating room personnel to contaminated items. One surgeon performs as much of the operation as possible. The handing off of instruments is kept to an absolute minimum. Rather than handing off contaminated needles to the scrub nurse, they are place directly on the Mayo stand. All disposable sharps are used once and then removed from the operative field. Needles are immediately cut from any tagged sutures. A clearly marked contaminated container is placed near the operating table, and all cotton swabs and blood-soaked waste are discarded by the surgeon directly.

Even though ophthalmic surgeons have less exposure to fluid than other surgeons, and seroconversion after needle sticks is uncommon, it seems prudent to minimize any potential nosocomial infections. We thank Drs. Ortiz and Aaberg for the concise summary of pertinent information and for bringing these important issues to the attention of the ophthalmic community.

ROBERT N. MAMES, M.D.
SCOTT M. FRIEDMAN, M.D.
Gainesville, Florida

Reply

EDITOR:

Doctors Mames and Friedman make valuable comments about dealing with known HIV-positive patients in the operating room. Their technique is an extension of the universal precautions recommended by the Centers for Disease Control. We agree with our colleagues and suggest that similar practices be used when dealing with patients whose HIV status is unknown. It is in this manner that the risk of transmitting HIV and other bloodborne pathogens can be minimized.

RAFAEL G. ORTIZ, M.D.
THOMAS M. AABERG, M.D.
Atlanta, Georgia

Anterior Chamber Aspirate Cultures After Uncomplicated Cataract Surgery

EDITOR:

In the article, "Anterior chamber aspirate cultures after uncomplicated cataract surgery," by J. B. Dickey, K. D. Thompson, and W. M. Jay (Am. J. Ophthalmol. 112:278, September 1991), 43% of anterior chamber aspirates in patients who had uncomplicated cataract extraction were culture-positive. None of these patients developed endophthalmitis, which, according to the authors, demonstrated the capacity of the anterior chamber to clear a low inoculum of bacteria after cataract surgery. Since subconjunctival gentamicin was administered at the conclusion of every operation, after fluid was aspirated from the anterior chamber for culture, is it not possible that the injected antibiotic rather than other factors discussed by the authors was responsible for the prevention of endophthalmitis?

P. SUNDERRAJ, F.R.C.S., E.C.Ophth.
Southport, England

Reply

EDITOR:

We thank Dr. Sunderraj for his thoughtful comments. The use of subconjunctival antibiotics at cataract surgery has been shown to reduce the rate of postoperative endophthalmitis in humans,[1] and to prevent the development of endophthalmitis in animal models where virulent organisms[2] or high inoculum doses were used.[3] However, since low endophthalmitis rates have been reported without the use of prophylactic antibiotics,[4] other factors probably also contribute to preventing postcataract endophthalmitis. Nevertheless, the finding of viable microorganisms within the anterior chamber of patients after uncomplicated cataract surgery is, in our opinion, a compelling argument for the use of prophylactic antibiotics.

JAMES B. DICKEY, M.D.
KENNETH D. THOMPSON, Ph.D.
WALTER M. JAY, M.D.
Maywood, Illinois

References

1. Chalkley, T. H. F., and Shoch, D.: An evaluation of prophylactic subconjunctival antibiotic injection in cataract surgery. Am. J. Ophthalmol. 64:1084, 1967.
2. Shockley, R. K., Fishman, P., Aziz, M., Yannis, R. A., and Jay, W. M.: Subconjunctival administration of ceftazidime in pigmented rabbit eyes. Arch. Ophthalmol. 104:266, 1986.
3. Elliot, R. D., and Katz, H. R.: Inhibition of pseudophakic endophthalmitis in a rabbit model. Ophthalmic Surg. 18:538, 1987.
4. Dunnington, J. H., and Locatcher-Khorazo, D.: Value of cultures before operation for cataract. Arch. Ophthalmol. 34:215, 1945.

Conjunctival Ophthalmomyiasis Caused by the Sheep Nasal Botfly *(Oestrus ovis)*

EDITOR:

To the interesting review and case reports in "Conjunctival ophthalmomyiasis caused by the sheep nasal botfly (*Oestrus ovis*)," by J. A. Cameron, N. M. Shoukrey, and A. A. Al-Garni (Am. J. Ophthalmol. 112:331, September 1991), I would like to add that at least five such cases occurred among American soldiers deployed to Saudi Arabia during Operation Desert Shield. Although these soldiers were in desert areas frequented by sheep, goats, or camels they did not have such close contact with them as did the subjects of the article.

In November 1990, one of these soldiers was treated at our Brigade Clearing Station. The soldier complained of a foreign-body sensation immediately after an insect flew toward his right eye. His eye was irrigated and treated for a mild corneal abrasion with sulfacetamide ointment and patched. The soldier returned four hours later complaining of pain in his right eye and movement under the patch. He had normal visual acuity, mild conjunctival erythema, and multiple 1-mm long white larvae. The eye was irrigated, treated with sulfacetamide ointment, and patched again. The still-living specimens were examined by U.S. Navy entomologists and identified as first in-star larvae of the sheep botfly, *Oestrus ovis*.

The following day the soldier still complained of a foreign-body sensation. Under examination with Wood's lamp, one more larva was detected in the inferior cul-de-sac. It was removed with a sterile cotton-tipped applicator. Copious irrigation disclosed no further larvae. The soldier remained asymptomatic. Results of ophthalmologic examination one month later were normal.

MAJOR PETER G. TOROK, M.D.
Fort Benning, Georgia

Reply

EDITOR:

The three patients with conjunctival ophthalmomyiasis caused by the sheep nasal botfly (*Oestrus ovis*), which we reported, all had a history of being in close proximity to sheep when they became symptomatic. As Dr. Torok and others[1,2] have noted, this history is not always present.

The case reported by Dr. Torok illustrates the potential problems in both the diagnosis and treatment of this condition. The larva, being translucent and measuring only 1 mm in length, may be difficult to detect, especially if it moves to the upper conjunctival fornix. A linear punctate keratitis caused by the larva as it moves across the cornea may be a valuable clue to the presence of this mobile foreign body. The case report emphasizes the need for follow-up examinations to ensure that all larvae have been removed with resolution of symptoms and signs.

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References

1. Harvey, J. T.: Sheep botfly. Ophthalmomyiasis externa. Can. J. Ophthalmol. 21:92, 1986.
2. Hennessy, D. J., Sherrill, J. W., and Binder, P. S.: External ophthalmomyiasis caused by *Estrus ovis*. Am. J. Ophthalmol. 84:802, 1977.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Basic Ophthalmology. An Interactive Videodisc Program. By T. A. Farrell and Educational Resources Group, Department of Ophthalmology, The University of Iowa, Iowa City, Iowa.

Reviewed by MARK MANNIS
Sacramento, California

For the past several years at the American Academy of Ophthalmology meeting, a course has been offered for individuals actively engaged in the teaching of ophthalmology to medical students. Despite the variety of pedagogic techniques that are demonstrated and discussed, there is always wishful mention of the application of sophisticated computer technology to the teaching of basic ophthalmology. Until now, however, such a comprehensive program has not been available to teaching institutions.

Basic Ophthalmology is a computerized, interactive, self-education package that uses standard computer technology into which laser videodisc technology has been artfully integrated.

The authors indicate that this teaching program is for medical students, family physicians, and other health care professionals and designed to provide them with the basic information they will need to treat patients who require routine eye care.

This is an interactive program that needs no prior special knowledge; the student participates in the instruction process and sets the pace. There are self-assessment exercises strategically placed along the route of instruction.

The program is divided into four chapters: Ocular Anatomy, Fundamentals of Vision, Assessment of Visual Loss, and Glaucoma. In the first of these chapters, the primary anatomic structures of the eye are described and illustrated with excellent computer graphics that can be enlarged by the student for study. The chapter on the fundamentals of vision deals largely with the basic eye examination. The chapter on assessing visual loss considers the differential diagnosis of acute and chronic visual loss and treatment. Finally, the chapter on glaucoma outlines the various types of glaucoma and how they can be diagnosed.

The Educational Resources Group at the University of Iowa has provided us with a unique format for self instruction in basic ophthalmology. The most appealing aspect of this program, aside from the way it requires the active participation of the student, is the inclusion of laser videodisc technology. Videodisc imagery is ideally suited both to demonstration of the ocular examination and to the presentation of specific ocular findings such as fundus photography. The description of the pupillary examination is dramatically enhanced by the video insert of an actual examination, which can be viewed repetitively by the student. Additionally, the ability to examine fundus photographs at different magnifications makes the illustrations much more useful than those found in a standard instructional text.

If there are any negative aspects to this program, they relate to the unevenness of its presentation. Some subjects are covered in much greater depth than others without apparent reason. For example, glaucoma seems to have received a disproportionate emphasis. In some areas of the program, such as the section on the evaluation of ocular motility, videodisc imagery was not used, and it might have been particularly helpful. There are several minor editorial problems such as spelling errors and at least one factual error. On the equipment I used, the program was relatively slow and required some patience. These drawbacks notwithstanding, Basic Ophthalmology is a good start to computer-based, self-instruction in ophthalmology.

Buyers should be aware of the hardware and software requirements for using the program. Requisite hardware includes an IBM PS/2 with a processor speed of at least 10 mHz, a minimum of 12 MB of hard disc storage, an IBM M-motion adapter board or IBM InfoWindow Display unit, mouse or touchscreen, and an NTSC standard videodisc player. Additional software requirements include the Learning System (LS/1) Presentation System, Version 1.0 and the L/S1 Language Extension-Presentation.

Strabismus. A Neurodevelopmental Approach. By John T. Flynn. New York, Springer-Verlag, 1991. 142 pages, index, illustrated. $65

Reviewed by LAWRENCE TYCHSEN
St. Louis, Missouri

After 25 years of clinical practice, Dr. Flynn took sabbatical leave from the Bascom Palmer Eye Institute. He spent that year in a little study carrel at the National Library of Medicine, reading and thinking about the cause of developmental strabismus. He says that this was a "catharsis, a cleansing and purification, and a journey . . . ." During the journey, he assembled his speculations into this short, remarkable book. The book is a blend of extended essay and fiery sermon, and to Dr. Flynn's credit, his personality shines through on every page.

What he preaches is that strabismus must be a cerebral miswiring problem; a miswiring that occurs because of one or several insults to the visual cortex, which occur prenatally and postnatally. If the insult is more severe it tends to show up earlier and the eyes usually turn in. Later, milder insults usually cause the eyes to turn out. He thinks that the miswiring probably involves the corpus callosum and a failure to eliminate exuberant, inappropriate connections between central and peripheral regions of the binocular visual field. All of this eventually affects a vergence center.

I have problems with only a few of the book's speculations. Carefully controlled experiments have now shown that the callosal connections are narrower in strabismic animals than in normal animals, not broader. Additionally, the most striking deficits in spatial perception and motion processing in strabismus occur under monocular, not binocular viewing conditions.

Dr. Flynn paints in broad strokes to provide a bird's-eye view of developmental strabismus. He wants to persuade the reader that, taken as a whole, the phenomenon of strabismus points away from muscles or even motor neurons and toward the cortex. Those seeking explicit neurophysiologic mechanisms, or cleanly delineated hypotheses supported by a chain of connected experimental findings, will not find them in this book. Dr. Flynn's purpose is rather to attract scientists suited to these tasks, and infect them with some of his own enthusiasm. The field could not have hoped for a more charismatic and convincing spokesman.

Books Received

Meeting the Needs of People with Vision Loss. A Multidisciplinary Perspective. By Susan L. Greenblatt. Lexington, Massachusetts, Resources for Rehabilitation, 1991. Softcover, 140 pages. $24.95 plus $3 shipping & handling.

When it becomes clear to the ophthalmologist that a patient's visual loss is irreversible, it is usually also evident to the patient. If the blindness is sudden, the ophthalmologist must be sensitive to the patient's bereavement and know how to be helpful. There is no need for the ophthalmologist to blunder into these situations, relying only on good will, human kindness, and common sense. Listening to others who have been there and preparing in advance are worthwhile actions, and this little book can be of help.

Veterinary Ophthalmology, ed. 2. Edited by Kirk N. Gelatt. York, Pennsylvania, Williams & Wilkins, 1991. 765 pages, index, illustrated. $125

This is the bible of veterinary ophthalmology. It was a substantial volume in the first edition a decade ago, and it is still a big book. There has been some shifting about and updating of the contents, and many chapters have been rewritten by new authors. Any ophthalmologist who works with animals will want to have access to this new edition of an important reference work.

ABSTRACT DEPARTMENT

Edited by Ronald M. Burde, M.D.

Decreasing severity of chronic uveitis in children with pauciarticular arthritis. Sherry, D. D.*, Mellins, E. D., and Wedgwood, R. J.: Am. J. Dis. Child. 145:1026, 1991.

We compared the current prevalence and severity of chronic uveitis in children with pauciarticular juvenile rheumatoid arthritis in Seattle, Wash, with that of children with the same condition in the same area in 1975. The prevalence of eye disease decreased from 45% in 1975 to 13% in 1989, and the proportion of patients with severe visual loss decreased from 21% in 1975 to none in 1989. We could not attribute these findings to differences in known risk factors for iritis, such as age, sex, or presence of antinuclear antibodies. There was no difference in the duration of follow-up between the two groups. It is possible that the decline in prevalence of uveitis reflects a referral bias for eye disease in the 1975 population. However, the decrease in disease severity remains unexplained and may represent more effective treatment, earlier surveillance for ocular disease, or a change in the frequency of ocular manifestations of this disease in the 1989 group.—Authors' abstract

*Division of Rheumatology, Children's Hospital and Medical Center, Seattle, WA 98105.

Trabeculectomies. A long-term study. Törnqvist, G.*, and Drolsum, L. K.: Acta Ophthal. 69:450, 1991.

This study comprises 277 primary open-angle glaucomas in 239 patients followed up to 10 years after trabeculectomy. Sixty-four percent had capsular glaucoma (pseudoexfoliation) and 36% simple glaucoma. The number of cases showing no progression of glaucoma damage and not needing additional medical therapy decreased slowly with time. Seventy-five percent showed no progress after one year, 70% after 2 years, 57% after 5 years and 42% after 10 years. There was a significant trend that fewer capsular glaucomas progressed than simple glaucomas. High pressure levels before trabeculectomy did not indicate a bad prognosis. Cases with advanced or moderate glaucomatous damage seemed to have the same prognosis. Cataract was a common complication; a 50% reduction of preoperative visual acuity was found in 37% of eyes after 5 years of follow-up.

*Department of Ophthalmology, Central Hospital, Skövde, Sweden.

Beneficial effect of sodium sucrose-sulfate on the ocular surface of patients with severe KCS in primary Sjögren's syndrome. Prause, J. U.*: Acta Ophthal. 69:417, 1991.

Sucralfate (aluminum sucrose-sulfate), a well known gastric mucosal protectant, has been tested topically on 22 patients (20 females and 2 males) suffering from primary Sjögren's syndrome. Median treatment period was 6 months (range 1–19 months). Statistically significant improvement in the ocular surface condition was found, judged from the reduction in Rose-Bengal score ($P \leq 0.00005$). The beneficial effect appeared within the first 1–4 months of treatment. No adverse side effects were encountered.—Author's abstract

*Eye Pathology Institute, University of Copenhagen, Denmark.

Identification of novel rhodopsin mutations associated with retinitis pigmentosa by GC-clamped denaturing gradient gel electrophoresis. Sheffield, V. C.*, Fishman, G. A., Beck, J. S., Kimura, A. E., and Stone, E. M.: Am. J. Hum. Genet. 49:699, 1991.

Retinitis pigmentosa is a group of disorders characterized by progressive degeneration of the outer retina, resulting in night blindness, visual field loss, an abnormal electroretinogram, and characteristic retinal pigmentary changes. An important step in the understanding of retinitis pigmentosa has been the recognition that some cases of autosomal dominant retinitis pigmentosa are caused by mutations in the rhodopsin gene. Multiple different point mutations within the coding sequence of the rhodopsin gene have been associated with autosomal dominant retinitis pigmentosa. We have developed a GC-clamped denaturing-gradient-gel electrophoresis assay for the coding region of the rhodopsin gene and have used this assay to screen autosomal dominant retinitis pigmentosa patients for mutations. The assay consists of amplifying with polymerase chain reaction, the five exons of the rhodopsin gene, and then analyzing each polymerase chain reaction product by denaturing-gradient-gel electrophoresis. We have used this assay to detect three previously unreported rhodopsin base substitutions associated with autosomal dominant retinitis pigmentosa. The use of this assay to identify autosomal dominant retinitis pigmentosa patients who have various rhodopsin mutations has allowed us to begin studies seeking to correlate molecular genotype with clinical phenotype. Furthermore, GC-clamped denaturing-gradient-gel electrophoresis has allowed us to identify families with autosomal dominant retinitis pigmentosa not caused by a rhodopsin mutation. Such families will be important in the search for other genes involved in autosomal dominant retinitis pigmentosa.

*Department of Pediatrics, 2615 JCP, University of Iowa Medical Center, Iowa City, IA 52240.

A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. Palestine, A. G., Polis, M. A., De Smet, M. D., Baird, B. F., Falloon, J., Kovacs, J. A., Davey, R. T., Zurlo, J. J., Zunich, K. M., Davis, M., Hubbard, L., Brothers, R., Ferris, F., Chew, E., Davis, J. L., Rubin, B. I., Mellow, S. D., Metcalf, J. A., Manischewitz, J., Minor, J. R., Nussenblatt, R. B., Masur, H., and Lane, H. C.*: Ann. Intern. Med. 115:665, 1991.

Objective. To evaluate foscarnet sodium in treating cytomegalovirus retinitis in patients with AIDS. *Patients.* Twenty-four previously untreated persons with AIDS and cytomegalovirus retinitis who were at low risk for loss of their visual acuity. *Intervention.* Patients were randomly assigned to receive either no therapy (delayed treatment, control group) or immediate treatment with intravenous foscarnet at a dose of 60 mg/kg body weight three times a day for 3 weeks (induction regimen) followed by a maintenance regimen of 90 mg/kg once a day. *Measurements.* Patients were examined weekly until they reached the primary clinical end point, defined as progression of their retinitis border by 750 μm or the development of a new retinal lesion due to cytomegalovirus. Progression was evaluated using retinal photographs by masked readers. Secondary evaluations included changes in visual acuity, cytomegalovirus shedding in the blood and urine, serum levels of human immunodeficiency virus type 1 (HIV-1) p24 antigen, and total CD4 T lymphocyte counts. *Results.* The mean time to progression of retinitis was 3.2 weeks in the control group ($n = 11$) compared with 13.3 weeks in the treatment group ($n = 13$) ($P < 0.001$). Nine of 13 patients in the treatment group had positive blood cultures for cytomegalovirus at entry and all nine cleared their blood of cytomegalovirus by the end of the induction period ($P = 0.004$) compared with one of six patients in the control group. No reductions in p24 levels were seen in the control patients compared with a reduction of more than 50% in p24 levels for all four patients on treatment for whom follow-up levels were available. The main adverse effects of foscarnet treatment were seizures (2 of 13 patients), hypomagnesemia (9 of 13), hypocalcemia (11 of 13), and elevations in serum creatinine above 176.8 μmol/L (2.0 mg/dL) (3 of 13). The control patients received an average of 0.2 units of blood per week compared with an average of 0.6 units of blood per week for the patients on treatment. *Conclusions.* The administration of foscarnet decreases the rate of progression of cytomegalovirus retinitis in persons with AIDS. Its judicious use is likely to prevent loss of vision in these patients. In this study, however, there was little change in visual acuity in patients in either the immediate or delayed treatment group because only patients with non-sight-threatening disease were selected.—Authors' abstract.

*National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 11B-13, Bethesda, MD 20892.

Trabeculectomy combined with β irradiation for congenital glaucoma. Miller, M. H., and Rice, N. S. C.*: Br. J. Ophthalmol. 75:584, 1991.

Sixty-six eyes with congenital glaucoma were subjected to trabeculectomy between July 1975 and June 1989 are presented. Thirty-one were treated with β irradiation at the time of surgery with a strontium-90 applicator; 35 were not treated with β irradiation. The usual dose was 750 rad. Analysis was limited to three years because of the shorter follow-up of the irradiated eyes. Failure in the two groups was compared statistically. When failure was categorised as IOP > 21 mm Hg, β irradiation was found to be significantly protective with adjusted risk ratio of 0.31 (95% confidence interval 0.11–0.90, $p < 0.05$). Failure categorised as the need for additional medical treatment or further surgery showed significant protection with an adjusted risk ratio of 0.33 (confidence interval 0.12–0.94, $p < 0.05$). Multiple regression models were used for the analysis of intraocular pressure; β irradiation was associated with a significantly lower IOP at six months, one year, and three years ($p < 0.05$). Other factors identified as being associated with a reduced failure rate or lower IOP were: no previous topical glaucoma medications; age over seven years; lack of previous surgery involving the conjunctiva. The results indicate that β irradiation may have a beneficial effect on the prognosis of trabeculectomy in children with congenital glaucoma. However, because of the retrospective and observational nature of the study, the results must be regarded as tentative.—Authors' abstract

*Moorfields Eye Hospital, City Road, London ECIV 2PD England.

Extraocular muscle surgery in myasthenia gravis. Acheson, J. F.*, Elston, J. S., Lee, J. P., and Fells, P.: Br. J. Ophthalmol. 75:232, 1991.

Myasthenia gravis is typically a disease of young people in active employment who need a field of binocular single vision. Although it is systemically controllable with a good chance of spontaneous remission, persistent loss of binocularity may cause chronic disability. We report our experience of extraocular muscle surgery in five patients with stable myasthenia gravis and persistent double vision. Extraocular muscle involvement was selective, giving rise to incomitant and concomitant squints, with individual muscle overaction as well as underactions. Treatment was by conventional recession and resection procedures with the additional use of Faden and adjustable sutures where appropriate. In all five cases a larger, stable field of binocular single vision was established. It is concluded that extraocular muscle surgery may be beneficial in selected cases of myasthenia gravis.—Authors' abstract

*Western Ophthalmic Hospital, Marylebone Road, London, NW1 5YE, England.

A prospective study on the treatment of retinoblastoma in 72 patients. Zelter, M.*, Damel, A., Gonzalez, G., Schwartz, L.: Cancer 68:1685, 1991.

Seventy-two patients with retinoblastoma (unilateral [47 patients] and bilateral [25 patients]) were studied for a period of 6 years. Treatment consisted of enucleation of those eyes that had severe involvement and was followed by radiation therapy and/or chemotherapy (systemic or intrathecal) according to clinical pathologic staging. All patients who underwent nonsurgical treatment received systemic chemotherapy. Intrathecal chemotherapy was administered when there was involvement of the central nervous system. Nonsurgical treatment consisted of radiation therapy and/or light coagulation, followed by enucleation if there was no response. The overall survival rates were 37 of 47 eyes (79%) for unilateral disease (median follow-up time, 63 months) and 18 of 25 patients (72%) with bilateral disease (median follow-up time, 81 months). Vision was regained in 14 of 21 conserved eyes.

*Ophthalmology Unit, Hospital de Niños de Buenos Aires, Buenos Aires, Argentina.

Blood-retina barrier permeability and its relation to the progression of diabetic retinopathy in type 1 diabetics. An 8-year follow-up study. Engler, C.*, Krogsaa, B., and Lund-Andersen, H.: Graefes Arch. Clin. Exp. Ophthalmol. 229:442, 1991.

Blood-retina barrier (BRB) permeability and its relation to the progression of diabetic retinopathy was studied over an 8-year period in 50 insulin-dependent diabetic patients. Initially, the patients underwent an ophthalmological examination, including measurement of best corrected visual acuity, fundus photography and vitreous fluorometry for determination of BRB permeability. After 8 years the patients were reexamined and their retinal status and clinical course were evaluated. We found a positive correlation between a high initial permeability value and an unfavorable clinical course using the parameter photocoagulation. A decrease in follow-up visual acuity was also associated with high initial permeability; however, this correlation was not statistically significant. A significant difference in mean blood pressure was found between values measured in laser-treated patients vs a group that did not undergo such therapy. Thus, in patients showing the same initial retinal morphology, high permeability seems to indicate an unfavorable disease course. The extent to which BRB permeability can be a valuable supplement to fluorescein angiography and three-mirror examination in the clinical decision process needs to be further evaluated.—Authors' abstract

*Department of Ophthalmology, University of Copenhagen, Gentofte Hospital, DK-2900 Hellerup, Denmark.

Epidemiology of glaucoma in Japan. A nationwide glaucoma survey. Shiose, Y.*, Kitazawa, Y., Tsukahara, S., Akamatsu, T. Mizokami, K., Futa, R. Katsushima, H., and Kosaki, H.: Jpn. J. Ophthalmol. 35:133, 1991.

A population-based, collaborative glaucoma survey was conducted in seven regions throughout Japan, during the years of 1988 and 1989. The total number of subjects examined was 8,126 out of 16,078 residents aged 40 years or older, representing a participation rate of 50.54%. There were no significant differences in background factors between participants and randomly sampled nonparticipants. A mainstay of the screening consisted of tonometry and fundus photography with nonmydriatic camera, followed by automatic perimetry as a recall examination. Overall prevalences obtained were primary open-angle glaucoma 0.58%, low-tension glaucoma 2.04%, primary angle-closure glaucoma 0.34%, other types of glaucomas 0.60%, and ocular hypertension 1.37% at the time of screening. The high prevalence of low-tension glaucoma and low prevalence of ocular hypertension in the Japanese might reflect a racial peculiarity in the age-specific trend of the intraocular pressure. The prevalence of primary angle-closure glaucoma was found much higher in Japanese than in Caucasians, with a predilection for women. Racial peculiarities as revealed in this study were discussed, with particular reference to the refractive status in the Japanese that showed progressive decrease in myopia with age.

*Division of Ophthalmology, Aichi Prefectural Center of Health Care, 3-2-1 Sannomaru, Naka-ku, Nagoya 460, Japan.

Therapy of Goldmann-Favre's vitreo-retinal degeneration with cyclosporin A and bromocriptine. Garweg, J., Böhnke, M., and Mangold, I.: Klin. Monatsbl. Augenheilkd. 199:199, 1991.

Several reports have described a disturbance of humoral and cellular immune response in patients with tapetoretinal degeneration, but a pathogenetic relation of the described immunological changes to the retinal disease was not established. Therefore immunosuppressive treatment has not been advocated for degenerative vitreoretinal disease. We report the natural course of Goldmann-Favre's vitreo-retinal degeneration and the results of a therapeutical trial with cyclosporin A and bromocriptine in two patients. Without therapy we saw a slowly progressive flat central retinoschisis with a serous macular exudation in fluorescein-angiography. Additionally we found peripheral vitreoretinal changes, mild cellular vitreal infiltration, extinguished electro-retinogram and disturbed dark adaptation. Visual acuity and visual field were quite stabile. Under therapy with cyclosporin A we found a regression of the macular edema and flattening of the retinoschisis. One of the two cases showed a good improvement of visual acuity, in the other case a clear subjective improvement did not correlate with an increase in visual acuity. An additional therapy with bromocriptine did not bring further success, but we were able to reduce the cyclosporine A to a blood concentration of 70–100 ng per ml.—Authors' abstract

*Universitäts-Augenklinik, Hamburg, Germany, and Universitäts-Augenklinik, Bern, Switzerland.

Correction of myopia with excimer laser keratomileusis. Seiler, T., Kriegerowski, M., Kahle, G., and Wollensak, J.*: Klin. Mbl. Augenheilkd. 199:153, 1991.

Results of excimer laser keratomileusis in 26 myopic sighted eyes are presented. The follow-up was at least 9 months. The base-line refraction was −4.48 ± 1.81 D (range: −1.4 to −9.25 D). After 3 months, 22 eyes (85%) were within ± 1 D from the intended refraction. The defined success rate after 6 months was 23 eyes (87.5%), after 9 months 25 eyes (88%), and after 12 months 24 eyes (92%). One month after surgery we found an overcorrection of +1.45 ± 1.22 D decreasing to +0.27 ± 0.94 D at three months, becoming an undercorrection of −0.24 ± 0.76 D after six, and −0.32 ± 0.69 D after nine months, and of −0.36 ± 0.6 D after one year. Stability within the measurement error (± 0.25 D) appeared in 20 (79%) of the treated eyes six months after treatment. Three patients have been excluded from the study group because they did not follow the protocol. Subepithelial haze occurred in all patients, becoming most intense after 3 months, gradually clearing over the next months. With appropriate steroid medication, the refractive effect may be modulated. Complications such as steroid glaucoma, recurrent erosion, loss of acuity, or extensive corneal scarring seem to be very rare.

*Augenklinik der Freien Universität Berlin im Klinikum, Charlottenburg, Berlin, Germany.

Diagnosis of *Chlamydia trachomatis* eye infection in Tanzania by polymerase chain reaction/enzyme immunoassay. Bobo, L.*, Munoz, B., Viscidi, R., Quinn, T., Mkocha, H., and West, S.: Lancet 338:847, 1991.

Detection of *Chlamydia trachomatis* eye infection is largely unsatisfactory by standard laboratory methods. A polymerase chain reaction/enzyme immunoassay that had previously been successful for diagnosis of genital *C. trachomatis* infection was compared with direct antibody immunofluorescence for detection of the organism in conjunctival scrapes. Two-hundred thirty-four Tanzanian children aged 1 to 7 years living in a village that had had no previous trachoma control programme were classified clinically as having no sign of trachoma (0) n = 97, follicular trachoma n = 100, or intense inflammatory trachoma with or without follicular trachoma (inflammatory trachoma ± follicular trachoma) n = 37. Polymerase chain reaction/enzyme immunoassay detected *C. trachomatis* in 24%, 54%, and 95% of subjects, respectively, compared with elementary body detection by direct antibody immunofluorescence of 1%, 28%, and 60%, respectively. Overall prevalence of chlamydial eye infection was 22% by direct antibody immunofluorescence compared with 48% by polymerase chain reaction/enzyme immunoassay. Of subjects with chlamydial DNA at pretreatment, 103 (92%) had no detectable chlamydial at the end of 4 weeks of ocular tetracycline. The findings show that polymerase chain reaction/enzyme immunoassay is likely to affect trachoma diagnosis and epidemiology because of the increased sensitivity for detection of *C. trachomatis* in all clinical groups; the less stringent requirements for specimen collection and transport make this method suitable for field use. Moreover, the semi-quantitative aspect of polymerase chain reaction/enzyme immunoassay may be useful for monitoring a decrease in chlamydial DNA after treatment.

*Department of Pediatrics, Division of Infectious Diseases, Wilmer Institute, Johns Hopkins School of Medicine, Baltimore, MD 21205.

Functional mapping of the human visual cortex by magnetic resonance imaging. Bellieau, J. W.*, Kennedy, D. N., McKinstry, R. C., Buchbinder, B. R., Weisskoff, R. M., Cohen, M. S., Vevea, J. M., Brady, T. J., and Rosen, B. R.: Science 254:716, 1991.

Knowledge of regional cerebral hemodynamics has widespread application for both physiological research and clinical assessment because of the well-established interrelation between physiological function, energy metabolism, and localized blood supply. A magnetic resonance technique was developed for quantitative imaging of cerebral hemodynamics, al-

lowing for measurement of regional cerebral blood volume during resting and activated cognitive states. This technique was used to generate the first functional magnetic resonance maps of human task activation, by using a visual stimulus paradigm. During photic stimulation, localized increases in blood volume (32 ± 10 percent, n = 7 subjects) were detected in the primary visual cortex. Center-of-mass coordinates and linear extents of brain activation within the plane of the calcarine fissure are reported.—Authors' abstract.

*Massachusetts General Hospital-NMR Center, 13th Street, Charlestown, MA 02129.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

International Society of Ocular Toxicology: Third Congress

The Third Congress of the International Society of Ocular Toxicology will be held Nov. 15–19, 1992, in Sedona, Arizona. Travel grants are available for young investigators. For more information, write Keith Green, Ph.D., Dept. of Ophthalmology, Medical College of Georgia, gusta, GA 30912-3400.

National Congress of the Sociedad biana de Oftalmologia

XXV National Congress of the Sociedad iana de Oftalmologia will be held July 992, in Santafé de Bogotá, Colombia, erica. For additional information, dad Colombiana de Oftalmologia, #100-20, Oficina 305, Santafé de mbia, South America.

thalmological Society: 78th er Seminar

Ophthalmological Society will nnual Summer Seminar on the August 1–5, 1992, at the Snow- e Center in Snowmass, Colo- nformation, write C.O.S., P.O. ewood, CO 80155; telephone

stitute: Welsh Cataract 92

Eye Institute at Baylor College of ill sponsor its Welsh Cataract Con- Sept. 10–12, 1992. For additional n, write Eula Mae Childs, Cullen Eye Baylor College of Medicine, 6501 Fannin (NC200), Houston, TX 77030; telephone (713) 798-5941; fax (713) 798-4364.

Manhattan Eye, Ear & Throat Hospital: Contact B & A Scan Ultrasonography for the Clinician

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a Contact B & A Scan Ultrasonography for the Clinician course April 4, 1992, at Sharp Cabrillo Hospital in San Diego, California. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Manhattan Eye, Ear & Throat Hospital: Fluorescein Angiography Workshop

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a Fluorescein Angiography Workshop April 4, 1992, in New York City. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Manhattan Eye, Ear & Throat Hospital: Genetic, Metabolic, and Toxic Diseases of the Retina

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold the Genetic, Metabolic, and Toxic Diseases of the Retina course March 21, 1992, in New York City. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Manhattan Eye, Ear & Throat Hospital: LuEsther T. Mertz Vitreous-Retina-Macula Lecture

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold the LuEsther T. Mertz Vitreous-Retina-Macula Lecture March 17, 1992, in New York City. The guest lecturer will be Robert Nussenblatt of the National Eye Institute, National Institutes of Health. Dr. Nussenblatt's lecture is entitled, "New approaches to the treatment of uveitis." For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Manhattan Eye, Ear & Throat Hospital: Ophthalmic Plastic Surgery Symposium

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold the Ophthalmic Plastic Surgery Symposium March 14, 1992, in New York City. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Manhattan Eye, Ear & Throat Hospital: Second Annual Eyelid Rejuvenation Symposium

The Manhattan Eye, Ear & Throat Hospital will hold the Second Annual Eyelid Rejuvenation Symposium May 8 and 9, 1992, in New York City. For further information, write Francine Leinhardt, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200, ext. 2776; fax (212) 832-9126.

Manhattan Eye, Ear & Throat Hospital: Sigmund Schutz Visiting Professorship

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold the Sigmund Schutz Visiting Professorship April 24 and 25, 1992, in New York City. Walter J. Stark, the Wilmer Institute, will be the guest lecturer. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Mericos Eye Institute: Sixth Annual Symposium—Visions in Ophthalmology '92

The Mericos Eye Institute of Scripps Memorial Hospital will sponsor its Sixth Annual Symposium—Visions in Ophthalmology '92 March 6 and 7, 1992, in La Jolla, California. For additional information, write Ellen Casey, Mericos Eye Institute, 5665 Oberlin Dr., Ste. 110, San Diego, CA 92121; telephone (619) 453-6222; fax (619) 535-3880.

Presbyterian Hospital of Dallas: 14th Annual Dallas Spring Ophthalmology Symposium

The Presbyterian Hospital of Dallas will sponsor the 14th Annual Dallas Spring Ophthalmology Symposium March 6 and 7, 1992, in Dallas, Texas. For further information, write Ashley Clark, Continuing Medical Education, Presbyterian Hospital of Dallas, 8200 Walnut Hill Ln., Dallas, TX 75231; telephone (214) 345-2323.

Retina Research Conference: Retina Workshop for General Ophthalmologists

The Retina Research Conference will sponsor a Retina Workshop for General Ophthalmologists April 10 and 11, 1992, in San Francisco, California. For further information, write Lorraine Geary, Retina Research Conference, P.O. Box 640370, San Francisco, CA 94164; telephone (415) 441-1057.

University of South Carolina: Ophthalmology Symposium

The Department of Ophthalmology at the
University of South Carolina will hold its Firs
Annual Ophthalmology Symposium in Colu
bia, South Carolina, March 27 and 28, 1992
more information, write Richard M. D
M.D., Course Director, South Carolina E
stitute, 4 Richland Medical Park, Ste. 10
lumbia, SC 29203; telephone (803) 254

University of Tennessee: 21st Annu Alumni-Residents Day Meeting

The Department of Ophthalmo
University of Tennessee Memph
Medicine will host the 21st An
Residents Day Meeting March
Memphis, Tennessee. For mor
write Roger L. Hiatt, M.D., Depa
thalmology, University of Tenn
Medicine, Health Sciences Ce
Ave., Memphis, TN 38163;
528-5883.

Tufts University School of Me Courses in Phacoemulsificatio

The New England Eye Center o
sity School of Medicine will spon
Annual Two Courses in Phacoe
March 27 and 28, 1992, in Boston,
setts. For further information, writ

O'Sullivan, New England Eye Center, 750 Washington St., Box 450, Boston, MA 02111; telephone (617) 956-5754.

Virginia Society of Ophthalmology: 1992 Annual Meeting

The Virginia Society of Ophthalmology will hold its 1992 Annual Meeting May 15 and 16, 1992, in Richmond, Virginia. For more information, write Donna Scott, 4205 Dover Rd., Richmond, VA 23221; telephone (804) 353-2721.

University of Washington School of Medicine: Diabetic Eye Diseases—Past, Present, and Future

The Department of Ophthalmology at the University of Washington will sponsor Diabetic Eye Diseases—Past, Present, and Future April 24 and 25, 1992, in Seattle, Washington. For further information, write the Office of Continuing Medical Education, University of Washington School of Medicine, 1325 Fourth Ave., Seattle, WA 98101; telephone (800) 869-2633 or (206) 543-1050.

Washington University Eye Center: 32nd Annual Spring Meeting

The Department of Ophthalmology and Visual Sciences of Washington University will hold its 32nd Annual Spring Meeting April 10, 1992, in St. Louis, Missouri. For more information, write Margo Long, Washington University Eye Center, 660 S. Euclid Ave., Box 8096, St. Louis, MO 63110; telephone (314) 362-3726; fax (314) 362-3725.

West Virginia Academy of Ophthalmology: 45th Annual National Spring Meeting

The West Virginia Academy of Ophthalmology will hold its 45th Annual National Spring Meeting April 23–26, 1992, in White Sulphur Springs, West Virginia. For more information, write Patricia Schumann, West Virginia Academy of Ophthalmology, P.O. Box 6302, WVU Health Sciences Center North, Morgantown, WV 26506; telephone (304) 293-3757.

West Virginia University: Third Annual Ophthalmology Alumni Weekend

The Department of Ophthalmology of the West Virginia University will hold its Third Annual Ophthalmology Alumni Weekend March 6 and 7, 1992, in Morgantown, West Virginia. For additional information, write Patricia Schumann, Dept. of Ophthalmology, WVU Health Sciences Center North, Morgantown, WV 26506; telephone (304) 293-3757.

Wilmer Ophthalmological Institute: Current Concepts in Ophthalmology and Hands-on Phacoemulsification Wet Lab

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor the Ninth Annual Current Concepts in Ophthalmology and Hands-on Phacoemulsification Wet Lab March 14–21, 1992, at the Manor Vail Lodge in Vail, Colorado. For additional information, write the Program Coordinator, Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 20, Baltimore, MD 21205-2195; telephone (301) 955-2959.

Wilmer Residents Association: 41st Association Meeting

The 41st Wilmer Residents Association Meeting will be held Apr. 30, May 1 and 2, 1992, in Baltimore, Maryland. The program director is Walter J. Stark, M.D. For further information, write Jo Ann L. Young, Wilmer 232, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

Pisart Vision Award: Call for Nominations

The Lighthouse Inc. is inviting nominations for its 12th annual Pisart Vision Award, a major U.S. prize given to people who have made a noteworthy contribution to the prevention, cure, or treatment of blindness or severe vision impairment. The $15,000 prize and accompanying sculpture is open to citizens of any country and will be presented in September 1992. For more information, write Secretary, Pisart Vision Award Committee, The Lighthouse Inc., 800 Second Ave., New York, NY 10017; telephone (212) 808-0077.

RP Foundation Fighting Blindness: Donor Eye Tissue Available

The RP Foundation Fighting Blindness sponsors histopathologic studies of donor eyes from patients with retinitis pigmentosa and other inherited retinal dystrophies and from obligate and suspected carriers of these disorders. Detailed histopathologic reports, including macrophotography and light and electron microscopy, have been generated on approximately

100 eyes and are now available to interested researchers. Tissue samples and sections from many of these donor retinas are available for distribution to qualified investigators. For more information, write Jill Hennessey, M.S., Retina Donor Program, RP Foundation Fighting Blindness, 1401 Mt. Royal Ave., Baltimore, MD 21217; telephone (410) 225-9400

Tissue Banks Research Program: Grant Applications

Tissue Banks International, the non-profit network of eye and tissue banks, invites the submission of proposals for funding of research related to corneal transplantation. Funding is envisioned primarily as seed money to develop ideas or to carry out key experiments leading to more extensive support by larger private or governmental agencies. For additional information, write Donald Ward, Technical Operations, TBI, 815 Park Ave., Baltimore, MD 21201; telephone (213) 223-0333.

American Society of Ophthalmic Plastic and Reconstructive Surgery: 1992 Officers

The American Society of Ophthalmic Plastic and Reconstructive Surgery has elected the following officers for 1992: John A. Burns, president; Albert Hornblass, president-elect; George L. Paris, vice president; Michael A. Callahan, executive secretary; Gerald J. Harris, treasurer; John A. Harrington, secretary; Perry F. Garber, secretary of education; John W. Shore, program chairman; Arthur S. Grove, Jr., chairman of Advisory Board.

National Institutes of Health Executive Council

Science (255:147, 1992) reports that National Institutes of Health director Bernadine Healy has appointed an executive council with each member having the status of deputy director. Named are Jay Moskowitz, associate director for science policy and legislation; John Diggs, deputy director for intramural research; Carl Kupfer, acting deputy director for intramural affairs; and John Mahoney, associate director for administration. Dr. Kupfer, also head of the National Eye Institute, will be off the executive body as soon as a permanent intramural chief is named.

Personal

Graham E. Trope

Graham E. Trope was appointed ophthalmologist-in-chief at The Toronto Hospital, and chairman of the Department of Ophthalmology at the University of Toronto, effective Jan. 1, 1992.